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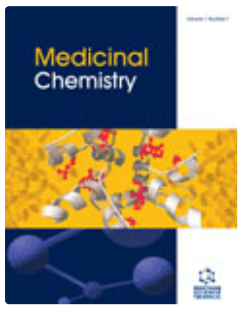

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Research Article

Computational Study and Synthesis of a New Class of Anticonvulsants with 6 Hz Psychomotor Seizure Test Activity: 2-(1,3-benzodioxol-5-yloxy)- N'-[substituted]-acetohydrazides

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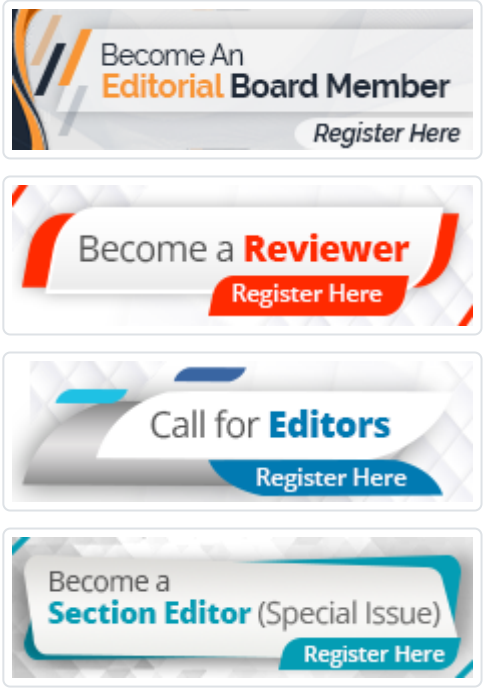

Abstract

Background: About 50 million epileptic cases worldwide and 12 million in India are reported. Currently, available drugs yield adequate control of seizure in 60-70% of patients and show many toxic effects. These actualities provoked the search for novel, more efficacious and safer anticonvulsants.

Objective: The concatenation of 2-(1,3-benzodioxol-5-yloxy)-N'-[substituted]-acetohydrazides SA 1- 10 was designed by molecular hybridization, optimized by computational study and synthesized with the objective of obtaining a prototype of potent anticonvulsant molecules especially active against partial seizures.

Methods: Computational study was performed to calculate the pharmacophoric design, projection of the pharmacokinetic parameters and docking scores of the titled compounds with molecular targets of epilepsy. The anticonvulsant activity was ascertained by 6 Hz psychomotor seizure test. Minimal motor impairment showing neurotoxicity was assessed using the Rotarod test.

Results: Titled compounds possessed the indispensable elements of pharmacophore and displayed good binding affinity with molecular targets of epilepsy, such as GABA (A) alpha-1 & delta receptor, glutamate receptor, Na+/H+ exchanger and GABA- aminotransferase in docking studies. The most potent compound of the concatenation was 2-(1,3-benzodioxol-5-yloxy)-N'-[4-(4- chlorophenoxy)benzylidene]-acetohydrazide SA 4, showing 100% protection at four different time points with ED_{50} value 146.8 mg/kg at a TPE of 1 h in mice.

Conclusion: The protection shown in 6 Hz test is implicated as the compound's ability to control partial seizures. Thus, the titled compounds can be considered as potential prototype candidates for antiepileptic therapy against partial seizures.

Keywords: 2-(1, 3-benzodioxol-5-yloxy)-N'-[substituted]-acetohydrazides, computational study, docking, synthesis, 6 Hz psychomotor seizure test, neurotoxicity.

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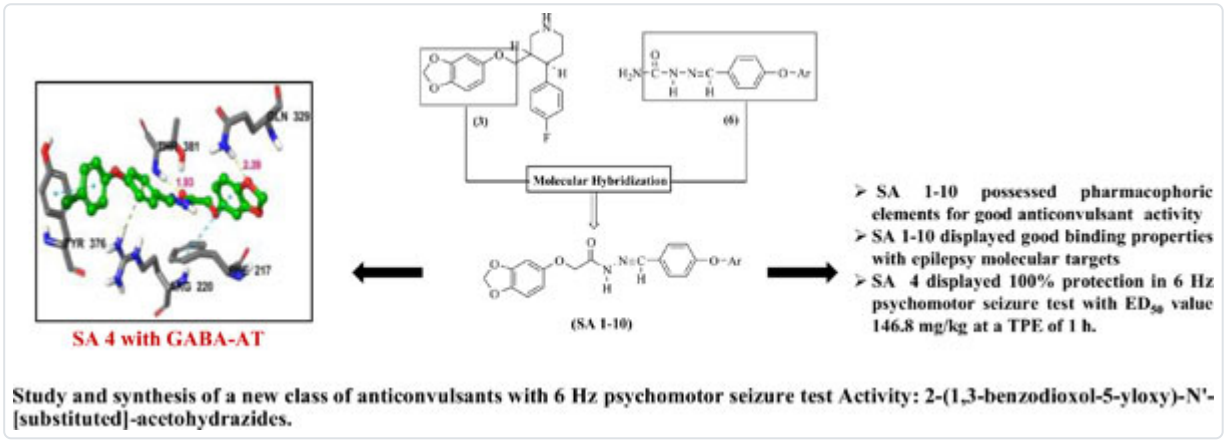

Study and synthesis of a new class of anticonvulsants with 6 Hz psychomotor seizure test Activity: 2-(1,3-benzodioxol-5-yloxy)-N'-[substituted]-acetohydrazides.

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Molecular dynamics analysis of phytochemicals from *Ageratina adenophora* against COVID-19 main protease (M^{pro}) and human angiotensin-converting enzyme 2 (ACE2)

Netra Prasad Neupane [a 1], Abhishek Kumar Karn [a 1], Imdad Husen Mukeri [a], Prateek Pathak [b], Praveen Kumar [c], Samayaditya Singh [d], Insaf Ahmed Qureshi [d], Tarun Jha [e], Amita Verma [a]

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Highlights

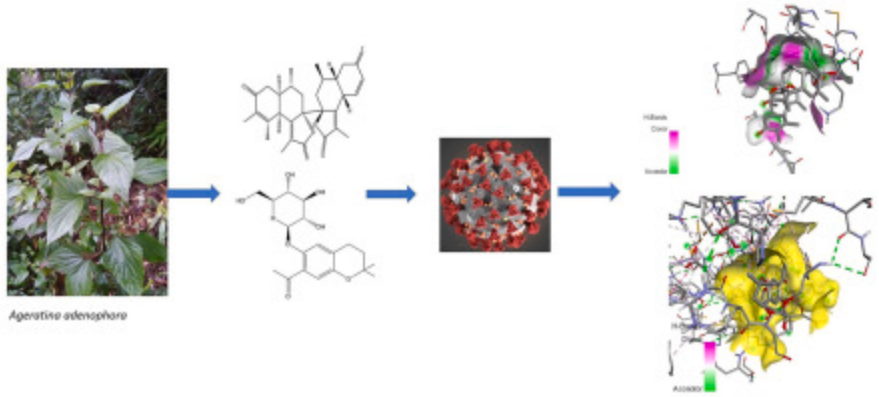
- The present study is designed to explore the 34 phytocompounds from *Ageratina adenophora* against SARS-CoV through *in-silico* studies.

- Molecular docking study with M^{pro} and ACE2 showed that phytocompounds from *Ageratina adenophora* have potential efficiency against COVID-19.
- MD simulations showed that GDE and BODO were found to be potential blockers with excellent binding affinity than their native inhibitors.
- The drug likeness study and pharmacokinetics of the phytocompounds provide an excellent support for the lead drug discovery against COVID-19.

Abstract

The outbreak of COVID-19 created unprecedented strain in the healthcare system. Various research revealed that COVID-19 main protease (M^{pro}) and human angiotensin-converting enzyme 2 (ACE2) are responsible for viral replication and entry into the human body, respectively. Blocking the activity of these enzymes gives a potential therapeutic target for the COVID-19. The objective of the study was to explore phytochemicals from *Ageratina adenophora* against SARS-CoV-2 through *in-silico* studies. In this study, 34 phytochemicals of *A. adenophora* were docked with M^{pro} and ACE2 through AutoDock Tools-1.5.6 and their binding affinity was studied. Phytochemicals with higher affinity have been chosen for further molecular dynamics simulations to determine the stability with target protein. Molecular dynamics simulations were studied on GROMACS 5.1.4 version. Furthermore, 5-β-glucosyl-7-demethoxy-encecalin (5GDE) and 2-oxocadinan-3,6(11)-dien-12,7-olide (BODO) were found to be potential blockers with excellent binding affinity with Mpro and ACE2 than their native inhibitors remdesivir and hydroxychloroquine respectively. The drug likeness study and pharmacokinetics of the phytoconstituents present in A. adenophora provide an excellent support for the lead drug discovery against COVID-19.

Graphical abstract



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Keywords

Ageratina adenophora; Angiotensin-converting enzyme; Main protease; Molecular docking; COVID-19

Abbreviations

5GDE
: 5-β-glucosyl-7-demethoxy-encecalin

DAOA
: 2-deoxo-2-(acetyloxy)-9-oxoageraphorone

OA

9-oxoagerophorone

ODO
: (+)-(5R,7S,9R,10S)-2-oxocandinan-3,6(11)-dien-12,7-olide

BODO
: (+)-7,7′-bis[(5R,7R,9R,10S)-2-oxocadinan-3,6(11)-dien-12,7-olide

HEDO
: (+)-(5R,7S,9R,10S)-7-hydroxy-7,12-epidioxycadinan-3,6(11)-dien-2-one

CED
: (−)-(5R,6R,7S,9R,10S)-cadinan-3-ene-6,7-diol

5-CQA
: 5-O-caffeoylquinic acid

3-CQA
: 3-O-caffeoylquinic acid

4-CQA
: 4-O-caffeoylquinic acid

M^{Pro}
: COVID-19 main protease

ACE2
: Human Angiotensin Converting Enzyme-2

MDPC
: methyl 3,4-bis[[(E)-3-(3,4-dihydroxyphenyl)prop-2-enoyl]oxy]-1,5-dihydroxycyclohexane-1-carboxylate

MDCQ

Methyl 3,5-di-O-caffeoyl quinate

1. Introduction

Coronavirus disease (COVID-19) caused by the novel coronavirus SARS-CoV-2 and declared as a global pandemic by WHO on March 11, 2020 (Ludwig and Zarbock, 2020; O'Horo, 2020). The first case of COVID-19 was reported in Wuhan, China in december (Tian et al., 2020). The virus is transmitted through direct or indirect contact of the respiratory droplet of an infected person and there is the possibility of air transmission (Brockmeier and Lager 2002; World Health Organization 2020). COVID-19 mainly affects the lungs and requires ventilator support in severe condition (NCT04382391, 2020). Signs and symptoms of infection include fever, dry cough, tiredness, ache and pain, sore throat, conjunctivitis, headache, loss of taste or smell, rash on the skin, or discoloration of fingers or toes (Sahai et al., 2020). SARS, MERS and SARS-CoV-2 belong to the same family, Coronaviridea (Chen et al., 2020). The outbreak SARS has infected 8096 and cause the death of 774 people (Bostancikliogl u 2020) and the MERS infect 2494 people and cause the death of 858 people. The recent outbreak of n-CoV-2 in November 2019, infect 62,686,326 and cause the death of 1,460,387 people globally till November 27, 2020. (Worldometers). The SARS-CoV-2 has a high mortality rate in the elder population, diabetes patients, people having cardiovascular diseases, and lungs diseases (Tskhay et al., 2020). Despite being so dangerous currently, there is no approved vaccine or drug for these viruses. Although hydroxychloroquine, lopinavir-ritonavir, favipiravir, remdesivir, tocilizumab are found effective in treating COVID-19 (Neupane et al., 2020)(Lu et al., 2020; Wu et al., 2020). Currently, several types of research and the clinical trial are going on worldwide to find the vaccine, but the success is still far away.

Structurally, SARS-CoV-2 consists of Spike glycoprotein (S), Envelope protein (E), Membrane protein (M), and Nucleocapsid protein (N). Coronaviruses bear positive-sense, single-stranded RNA (+ssRNA) genetic material with approximately 30,000 nucleotides, the longest identified genome in RNA viruses till date (Malik 2020). Viral genome of SARS-CoV-2 consists of 14 open reading frames (ORFs) (Bhosale et al., 2012). Among which the main reading frame ORF1ab encodes for two overlapping polyproteins 1a (pp1a) and replicase polyprotein 1ab (pp1ab) (Cowley et al., 2000). These polyproteins play a major role in the replication and transcription of the viral genome (Robb et al., 2009). The virus has a protease class of hydrolytic enzyme known as Main protease (M^{pro}) also called as chymotrypsin-like protease (3CLpro). The entry of virus in the host has mediated binding Spike protein with human angiotensin-converting enzyme receptor-2 (ACE2) (Wan et al.,

2020). Inside the host cell, proteolytic cleavage of pp1a and pp1ab by SARS-CoV-2 M^{pro} give rise to numerous non-structural proteins like RNA dependent RNA polymerase (RdRp), helicase and non-structural protein 3, 4, and 6 (nsp3, nsp4, and nsp6). These non-structural proteins are thought to be responsible for coronavirus replication. Thus, M^{pro} has emerged as important drug targets (Kirchdoerfer and Ward 2019) and as there is a very low similarity with human proteases and SARS-CoV-2 protease, inhibitors of M^{pro} will be very less toxic to humans. Human angiotensin-converting enzyme-2 (ACE2) is another potential target as it is directly involved in the entry of the virus into the host cell. ACE2 belongs to the angiotensin-converting enzyme family of dipeptidyl carboxydipeptidase. ACE2 protein catalyses the angiotensin I into angiotensin 1-9 and angiotensin II into the angiotensin 1-7. The ACE2 protein is a functional receptor for the spike glycoprotein of coronavirus diseases-2019 (COVID-19). (Magrone et al., 2020; Wan et al., 2020).

A. adenophora (commonly known as Crofton weed) is a perennial, semi-shrubby herbaceous plant which belongs to the Asteraceae family (Zhu et al., 2007). The plant is introduced as an ornamental plant, but leaf extract of the plant is found to have antimicrobial, antiseptic, analgesic, antipyretic, anti-inflammatory, larvicidal, insecticidal, wound healing, antitumor, and also antiviral activity (Poudel et al., 2020). Different research showed leaf extracts of *A. adenophora* have potential anti-viral activity against tobacco mosaic virus (TMV) and Human Immune virus (HIV). Jin et al. investigated antiviral activities of Eupatorium adenophorum leaf extract and it inactivated TMV particles and also effective in slight curative as well as preventive purpose (Jin et al., 2014). Ma et al. also suggested that *A. adenophora* has anti-HIV activity(MA et al., 2015). This excited us to do the in-silico screening of *A. adenophora* phytochemical in search of cheaper and less toxic phytochemicals against COVID-19 (André et al., 2019; Jin et al., 2014). Phytochemical screening reported that *A. adenophora* consist various class of secondary metabolites *such as* terpenoids, phenylpropanoids, flavonoids, coumarins, essential oils, sterols, phenolic acids, and alkaloids (Poudel et al., 2020; He et al., 2020). Among all the phytochemicals of *A. adenophora*, 34 phytochemicals were screened and docked with main protease (M^{pro}) of SARS-CoV-2 and angiotensin-converting enzyme receptor-2 (ACE2) of humans and results were compared with standard drugs which are found effective against SARS-CoV-2.

2. Methodology

2.1. Receptor preparation

The crystal structure of a COVID-19 main protease (M^{pro}) and human angiotensin-converting enzyme-2 (ACE2) related carboxypeptidase has been downloaded from protein data bank (PDB) website (http://www.rcsb.org/pdb↗)(Berman et al., 2000) (PDB ID: 6LU7↗ and 1R42↗) and were prepared by using Autodock tools-1.5.6. Kollman charges were added to each atom, non-polar hydrogens were merged, atom types were determined, and the structure of the prepared receptor were saved as pdbqt file.

2.2. Ligand preparation

The list of the major phytochemicals of *A. adenophora* were retrieved from the earlier reported literature (Poudel et al., 2020). The structures of known major chemical components of the plant were prepared using Chemdraw 3D pro12.0. software (Cousins 2005)and built - and - edit module in Open Babel 2.2.3 tool(O'Boyle et al., 2011). MMF F94s force field parameters were assigned to ligands atoms and then the energy has been minimized. Kollman charges were added to each ligand atoms. However, nonpolar hydrogen atoms were merged, and rotatable bonds defined. The structure of the ligands was saved in pdbqt format and used as in put ligand file for Autodock in docking.

2.3. Active site selection

The active site of the COVID-19 M^{pro} protein (PDB ID: 6LU7↗) and Human ACE2 protein (PDB ID: 1R42↗) has been predicted from different receptor cavities available. The different active site was identified from Discovery Studio 2020 (BIOVIA) client among these, site 1 of COVID-19 Mpro with coordinates (X=−10.711837, Y=12.411388 and Z=68.831286) and ACE2 receptor with coordinates (X=44.98, Y=20.98 and Z=16.80) have been chosen as the active site.

2.4. Virtual molecular docking

The receptor and ligand interaction through virtual molecular docking have been performed through AutoDock Tools-1.5.6. All the molecules have been docked to active site 1 of COVID-19 M^{pro} and active site 1 of ACE2 receptor. Ligand-receptor interaction was viewed through Discovery Studio 2020 Client (BIOVIA) and re-docking of all the compounds was done to assure reproducibility (Pathak et al., 2020).

2.5. Molecular dynamic simulation

The effects of the ligands on the structural dynamics of proteins were studied on GROMACS 5.1.4 version (Abraham et al., 2015). Each complex and apo forms of the M^{pro} and ACE2 proteins were considered for the study. Additionally, the protein and water topology were defined by GROMOS43A2 force field (van Gunsteren et al., 1996) and SPC/E water model (Berendsen et al., 1987), respectively. Each ligand topology was generated through the same force field using the PRODRG server (http://prodrg2.dyndns.org/submit.html). The charge of each simulating system was neutralized by an appropriate number of sodium ions (Na^+). Subsequently, the energy of the simulating systems was minimized by the steepest descent algorithm in 50,000 steps. The two-phase equilibration of 100ps was carried out by NVT (at constant 300K) and NPT (at constant 1 bar) ensemble equilibrations for each system. Consequently, MD simulation of 50ns was carried out for each system and the data was used for the enumeration of RMSD, RMSF and Rg. Furthermore, the binding energy was enumerated by the gMMPBSA package (Kumari et al., 2014) of GROMACS for every 0.1 ns frame of the last 20ns simulation of each protein-compound complex.

2.6. Drug likeness property

Physicochemical and pharmacokinetic properties to different phytochemical present in *A. adenophora* were studied using Swiss ADME a free online web tool (Zoete et al., 2016) (http://swissadme.ch/) by submitting their respective structures.

3. Result and discussion

3.1. Virtual screening through molecular docking

The SARS-CoV-2 M^{pro} with N3 inhibitor is divided into three domains. Domain I (from Phe 8 to Try 101), domain II (from Lys 102 to Pro 184) and domain III (from Thr 201 to Val 303). Domain I and II have an anti-parallel β-barrel structure. Domain III contains five α-helices arranged into the large anti-parallel globular cluster and is connected with domain II through loop region, which consist residue from Phe 185 to Ile 200. The substrate-binding site of M^{pro} of SARS-CoV-2 has Cys-His catalytic dyad, where N3 inhibitors bind. This is located in the cleft between domain I and domain II. Fig. 1 represents the crystal structure of COVID-19 main protease (M^{pro}) in complex with an inhibitor N3 and three domains of M^{pro}.

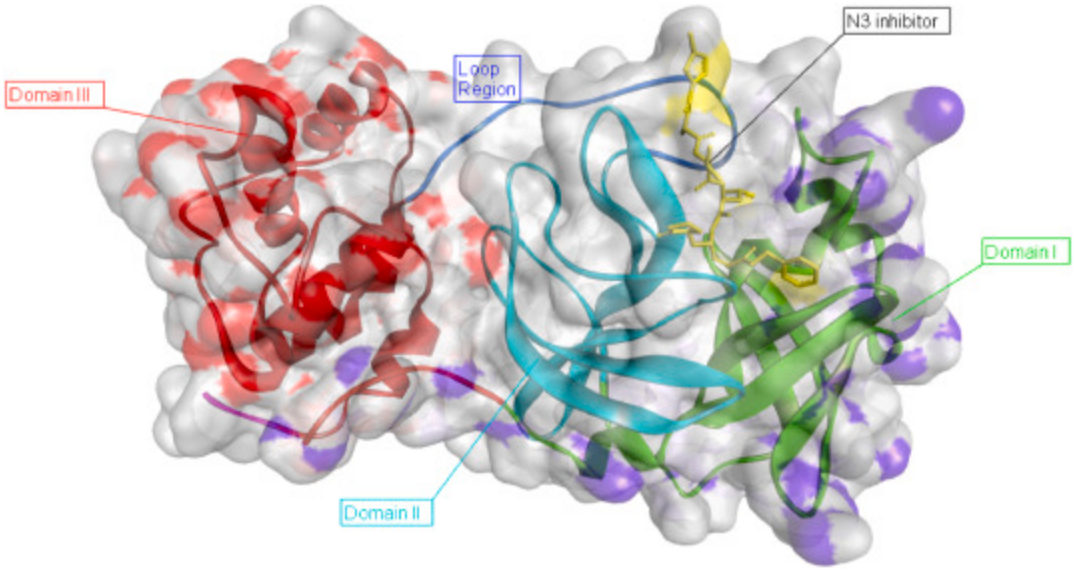

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Fig. 1. Crystal structure of COVID-19 main protease (M^{pro}) in complex with an inhibitor N3. Domain I shown in green, Domain II shown in cyan, Domain III is shown in red, and loop region shown in blue. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

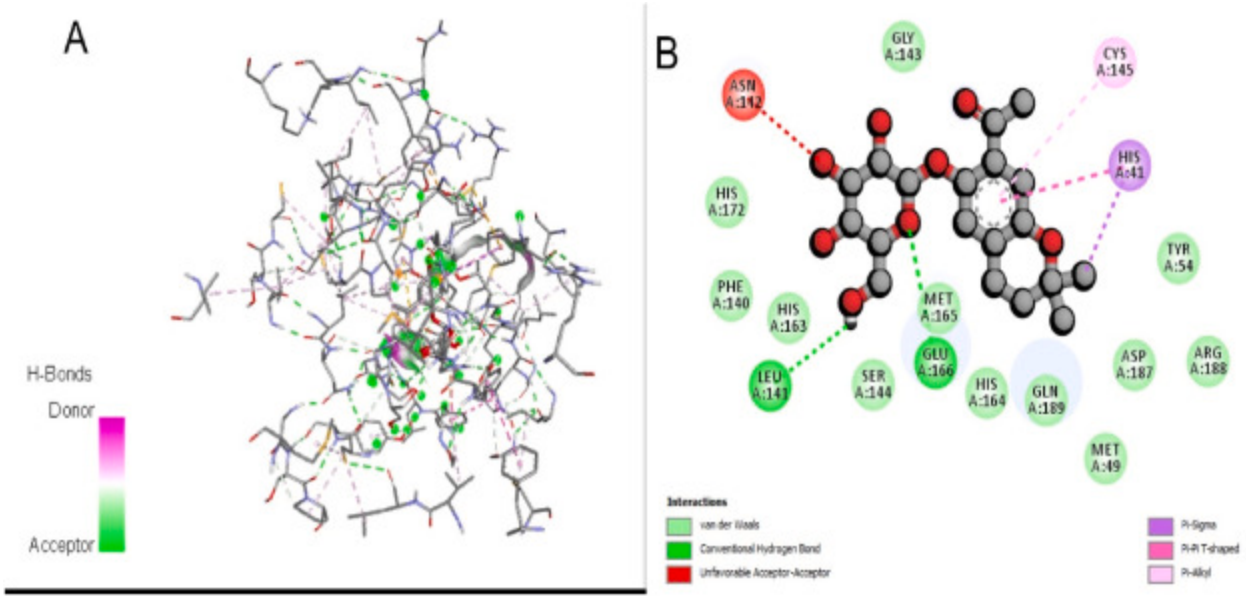

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Fig. 2. (A) The phytocompound 5GDE M^{pro} complex. (B) Detail amino acid interaction of 5GDE complex with M^{pro} in 2D.

The validation of the docking calculation was evaluated by redocking M^{pro} inhibitor remdesivir on the main protease protein of SARS-CoV-2 (PDB ID: 6LU7↗). It displayed that remdesivir is able to bind in the almost same pose in the same binding pocket with a binding affinity of −7.8 kcal/mol. The study showed that remdesivir interacts with M^{pro} through various types of interaction with different amino acid residues by making hydrogen bond and Van der Waals bonds. However, it was noticed that the tested ligands interact with Glu A:166, Leu A:141, Gly A:143, Ser A:144, and Cys A:145 amino acids through hydrogen bonds.

The interaction between phyto compound 5GDE and M^{pro} receptor is displayed in Fig. 2.

These interactions are compared with native inhibitor N3 and it was found that 90.90% amino acid showed similarity with that of a co-crystal ligand, which was found acceptable. Thus, the protein was further utilized for docking 34 different compounds reported in *A. adenophora* and docking score is displayed in Table 1 (Poudel et al., 2020).

Table 1. Docking score of 34 phytochemicals present in *A. Adenophora* with Main protease protein (M^{pro}) and human ACE2.

S.N	Phytochemicals	Docking score of M^{pro} (affinity Kcal/mol)	Docking score of human ACE2 (affinity Kcal/mol)
1	7-hydroxy-dehydrotremetone	-6.3	-5.7
2	7,10,11-trihydroxy dehydrotremetone	-6.6	-6.2
3	10-oxo-7-hydroxy-nordehydrotremetone	-6.2	-5.7
4	2αmethoxyl-3β-methyl-6-(acetyl-O-methyl)-2,3-dihydrobenzofuran	-5.7	-5.3
5	5-b-glucosyl-7-demethoxy-encecalin (5GDE)	-8.1	-6.5
6	8-hydroxy-8-b-glucosyl-2-carene	-6.6	-5.7
7	(4S,4aR,6R)-1-acetyl-6-(acetyloxy)-4,4a,5,6-tetrahydro-4,7-dimethylnaphthalen-2(3H)-one	-6.6	-5.7
8	2-deoxo-2-(acetyloxy)-9-oxoageraphorone(DAOA)	-6.2	-6.0
9	9-oxoagerophorone(OA)	-5.9	-5.3
10	9-oxo-10,11-dehydro-agerophorone(ODA)	-6.0	-5.9
11	9β-hydroxy-ageraphorone	-5.8	-5.4
12	Muurol-4-en-7-ol	-5.7	-5.5
13	8-beta-hydroxy-9,12-dehydroverbocciolenten	-5.5	-5.2
14	2 β-acetoxy-(7α, 9β H)-3.6(11)-cadinadien-12(7)-olide	-6.9	-6.4
15	3-hydroxymuurola-4,7 (11)- dien-8-one	-6.1	-5.5
16	(+)-(5R,7S,9R,10S)-2-oxocandinan-3,6(11)-dien-12,7-olide (ODO)	-6.8	-6.5

S.N	Phytochemicals	Docking score of M^{pro} (affinity Kcal/mol)	Docking score of human ACE2 (affinity Kcal/mol)
17	(+)-7,7′-bis[(5R,7R,9R,10S)-2-oxocadinan-3,6(11)-dien-12,7-olide (BODO) (He et al., 2008)	-6.3	-8.8
18	(+)-(5R,7S,9R,10S)-7-hydroxy-7,12-epidioxycadinan-3,6(11)-dien-2-one (HEDO)	-6.7	-6.3
19	(−)-(5R,6R,7S,9R,10S)-cadinan-3-ene-6,7-diol (CED)	-5.8	-5.5
20	(+)-(5S*,6R*,9R*,10S*)-5,6-dihydroxycandinan-3-ene-2,7-dionel	-6.0	-5.7
21	7-hydroxycandinan-3-ene-2-one	-5.6	-5.4
22	5,6-dihydroxy candinan-3-ene-2,7-dione	-6.5	-5.9
23	2-acetyl-candinan-3,6-diene-7-one	-6.1	-6.1
24	Candinan-3-ene-2,7-dione	-5.8	-5.3
25	Candinan-3,6-diene-2,7-dione	-6.2	-5.6
26	1,6-dihydroxy-1-isopropyl-4,7-dimethyl-3,4dihydronaphthalen-2(1H)-one	-6.4	-5.8
27	(4R,5S)-4-Hydroxy-5-isopropyl-2-methyl-2-cyclohexehone	-4.9	-4.6
28	5-O-caffeoylquinic acid (5-CQA)	-7.2	-6.3
29	3-O-caffeoylquinic acid (3-CQA)	-8.0	-6.4
30	4-O-caffeoylquinic acid (4-CQA)	-7.6	-6.4
31	5-O-trans-o-coumaroylquinic acid methyl ester	-7.0	-6.3
32	methyl (1*R*,3*S*,4*S*,5*S*)-3-[(*E*)-3-(3,4-dihydroxyphenyl)prop-2-enoyl]oxy-	-7.3	-6.2

S.N	Phytochemicals	Docking score of M^{pro} (affinity Kcal/mol)	Docking score of human ACE2 (affinity Kcal/mol)
	1,4,5-trihydroxycyclohexane-1-carboxylate		
33	methyl 3,4-bis[[(*E*)-3-(3,4-dihydroxyphenyl)prop-2-enoyl]oxy]-1,5-dihydroxycyclohexane-1-carboxylate (MDPC)	-7.4	-7.3
34	Methyl 3,5-di-O-caffeoyl quinate (MDCQ)	-8.0	-6.8

It was found that among these only three compounds (5GDE, 3-CQA and MDCQ) have better binding affinities than remdesivir. Moreover, 5GDE showed the highest docking affinity (−8.1 kcal/mol) in the entire set of molecules. The comparison between remdesivir and phytocompound 5GDE complex displayed 100% similarity in interaction pattern, illustrated in Table 2. Among all the interacting amino acids of 3-CQA and MDCQ it was found that 94.11% and 94.73% amino acid interactions are similar with remdesivir, respectively. The docking score along with hydrogen bond and Van der Waals interactions of these three compounds with M^{Pro} is shown in Table 2.

Table 2. Molecular interaction of top 3 high scoring compounds with Main protease protein (M^{pro}) of SARS-CoV-2.

S.N.	Compounds	H-bond interactions	Van der waals interactions
1.	5GDE	LEU A:141, GLU A: 166	MET A:49, TRY A:54, ARG A:188, ASP A:187, GLN A:189, SER A:144, MET A:165, SER A:144, HIS A:163, PHE A:140, HIS A:172, GLY A:143
2.	3-CQA	GLU A: 166, CYS A: 145, THR A: 190	HIS A:172, PHE A:140, LEU A:141, ASN A:142, SER A:144, GLN A:189, ARG A:188, GLN A:192, ALA A:191, PRO A:168, HIS A:164
3	MDCQ	LEU A:141, HIS A:163, SER A:144, SER A:144, GLN A:192	PHE A:140, ASN A:142, GLY A:143 TRY A:54, ASP A:187, ARG A:188, GLN A:189, THR A: 190, LEU A:167, GLN A: 166

The human ACE2 enzyme is composed of two domains; the first is zinc metallopeptidase domain depicted in Fig. 3(residues 19–611) and the second C terminus domain (residues 612–740). The first domain is 42% identical to the corresponding

domains of humans ACE. The first zinc metallopeptidase domain is located near the bottom and on one side of the large active site cleft. The zinc is coordinated by His374, His 378, Glu402 and single water molecules (in the native structure). The second domain is identical to human collectrin by 48%. The ACE2 metallopeptidase domain was divided into two subdomains (I and II), that formed the two sides of a long deep cleft with dimensions of40 A˘ long by 15A˘ wide by 25A˘ deep. The catalytic subdomains are only connected at the floor of the active site cleft.

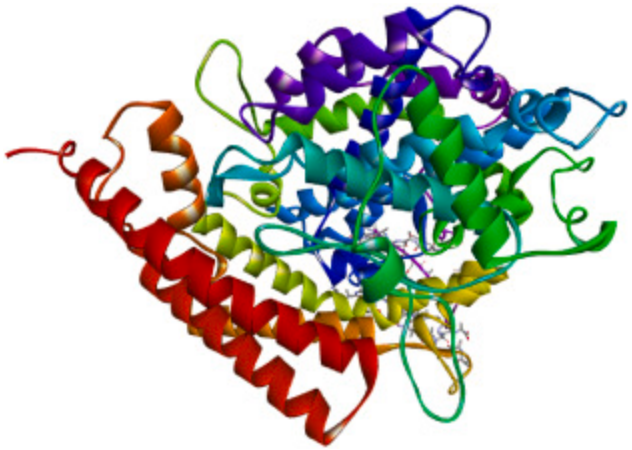

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Fig. 3. The crystal structure of COVID-19 zinc metallopeptidase domain of ACE2 (PDB ID: 1R42↗). Surface is created around the co-crystal ligand present in the binding pocket in which docking is performed for the study.

Initially, re-docking of the endogenous or native co-crystal ligand has been performed for the validation of the whole docking procedure ensuring its reproducibility. A total of 34 phytochemicals of *A. adenophora* have been docked with human ACE2. The receptor-ligand interactions have indicated that all the compounds used for docking procedure have a substantial binding affinity among them top 5 high scoring compounds are listed in Table 3.

Table 3. Enlisting of molecular interactions of top 5 high scoring *A. adenophora* phytochemical with human ACE2 protein.

S.N.	Compound Name	Hydrogen bond	Van der Waals interaction
1	BODO	-	UNK C:909, PRO A: 492, TYR A:613, GLU A:495, GLU A:489, TRP A: 478, HIS A: 493, ASP A:494, LYS A:475, UNK C:907, MET A:474
2	MDPC	TYR A:613, ARG A:482, ASP A:471, GLU A:489	UNK C:910, UNK C:909, ASP A:615, SER A:611, ASP A:609, ASP A:494, HIS A:493, GLN A:472, TRP A:478
3	5GDE	HIS A:493	-
4	ODO	ARG A:482	TRP A:478, PRO A:492, GLU A:489, THR A:608
5	MDCQ	HIS A:493, GLU A:479	SER A:611, ALA A:614, TYR A:613, UNK C:909, ARG A:482, TRP A:478, UNK C:908, UNK C:907, MET A:474, ASP A:494

Top 5 high scoring compounds has been taken into consideration for further detailed analysis as reflected in Table 3. BODO has shown the best binding affinity towards the human ACE2 receptor with a binding energy of −8.7 kcal/mol. This binding energy is higher than best fit inhibitor (Hydroxychloroquine) binding affinity, which is −6.3 kcal/mol. The best fit inhibitor was selected by comparing binding affinity of several drugs that have shown activity against COVID-19. The interaction of the compound with the human ACE2 receptor is depicted in Fig. 4. Docking study has exhibited that BODO interacts with 11 amino acid residue among which 7 residues (GLU A:495, ASP A:494, PRO A:492, HIS A:493, TRP A:478, TYR A:613, GLUA:489) matches with that to the inhibitor hydroxychloroquine. Thus, can be predicted compound binds to the receptor properly to inhibit human ACE2 protein.

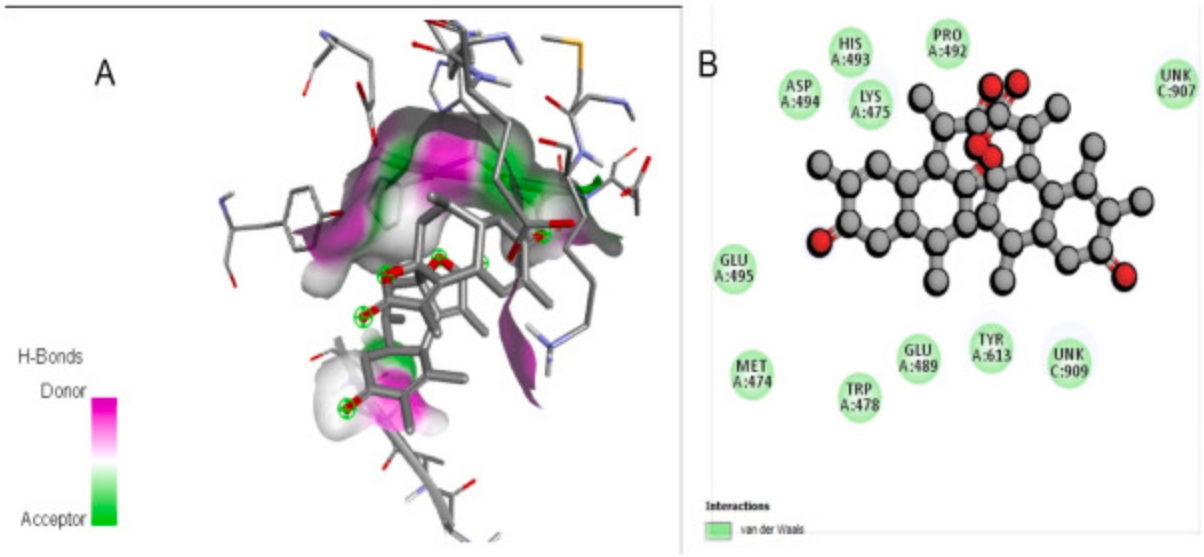

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Fig. 4. (A) The phytocompound BODO ACE2 complex. (B) Detail amino acid interaction of BODO with ACE2 receptor in 2D.

MDPC, a phytochemical of *A. adenophora,* has shown a binding energy score of −7.5 kcal/mol, which is higher than the native inhibitor. The study stated that MDPC interacted with 10 amino acid residues (TYR A:613, ARG A:482, GLU A:489, ASP A:494, ASP A:471, HIS A:493, TRP A:478, GLN A:472, GLU A:495 and GLU A:479), which matches with the hydroxychloroquine. Further, it was also noticed that 5GDE have higher binding affinity (−6.7 kcal/mol) with human ACE2 than native inhibitor hydroxychloroquine. Additionally, the careful study of interaction emphasized that the compound 5GDE interacts with two amino acids through hydrogen and pi-alkyl bonds, where one amino acid residue HIS A: 493 found common to the native hydroxychloroquine.

A. adenophora phytochemical have already proven anti-TMV and anti-HIV activity. In our in-silico study molecular dynamics of phytochemicals of *A. adenophora* done with M^{pro} and ACE2 virtually and found that phytochemicals BODO and 5GDE, were potential blockers of M^{pro} and ACE2. These plant materials are extremely abundant, convenient to harvest and easy to collect. This will lead to cost effective drug can be develop.

3.2. Molecular dynamic simulation

To elucidate the effects of the selected compounds (BODO and 5GDE) on the structural attributes of the respective protein (ACE2 and M^{pro}), the comparative MD analysis was carried out between each protein complex and its apo form. The average RMSD of M^{pro} complex and apo form was enumerated as 0.37, and 0.29 nm, wherein M^{pro} exhibited low deviations in backbone atoms with 5GDE in comparison to the apo structure. The RMSD graph is displayed in Fig. 5.

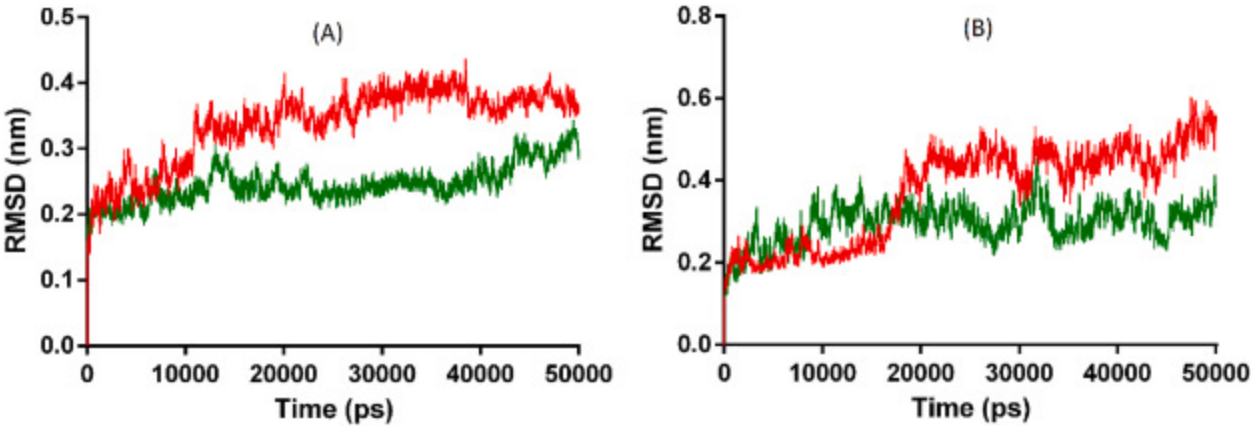

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Fig. 5. A and B displayed RMSD of ACE2 and M^{pro}.

Further, the effect of interaction between compound and M^{pro} protein on its compactness was analyzed by Rg analysis. The respective average Rg values were computed as 2.14 and 2.15 nm for apo and complex form, suggesting that both forms exhibited a similar level of compactness during simulation. The backbone atom fluctuation of the M^{pro} residues in both forms was analyzed by the RMSF data, which showed that apo and complex form have an average RMSF of 0.21 and 0.15 nm, respectively. It indicates that backbone atoms of M^{pro} residues showed low fluctuation in complex form in comparison to the apo form. The MD analysis showed that the M^{pro} complex structure retains similar compactness like its apo structure, but with increased structural stability and low residue fluctuation in comparison to the apo form during the simulation. Analysis also depicts the stability of interactions between 5-β-glucosyl-7-demethoxy-encecalinand protein during the dynamics.

Simultaneously, the average RMSD of the respectiveACE2 complex and apo form was enumerated as 0.34, and 0.25 nm that delineate lesser deviations in the backbone atoms of the ACE2-compound complex in comparison to its apo structure. The effect on compactness of the ACE2 after accommodating the BODO was analyzed through Rg analysis. The average Rg value for the ACE2 apo and complex form was found to be 2.47 and 2.46 nm, respectively, indicating that both apo and complex forms of ACE2 protein attained a similar level of compactness. The Rg graph is displayed in Fig. 6.

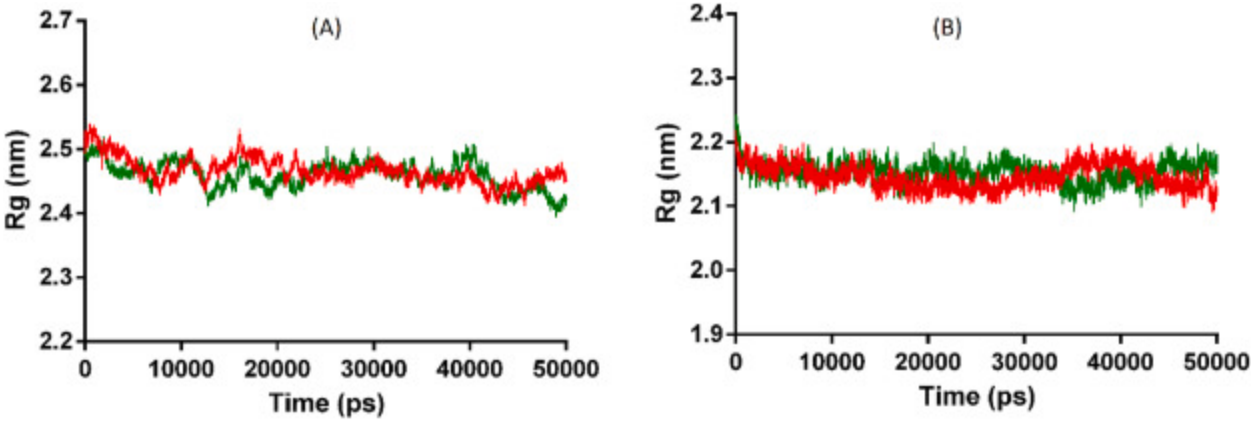

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Fig. 6. (A) and (B) displayed Rg of ACE2 and M^{pro}.

The backbone atom fluctuation of the ACE2 residues was analyzed by the RMSF data, which showed similar levels of fluctuation in apo and complex forms with an average RMSF of 0.15 and 0.14 nm, respectively. The MD analysis showed that the ACE2 complex structure retains similar compactness and residues motion like its apo structure, but with increased structural stability during the simulation. The RMSF graph is displayed in Fig. 7.

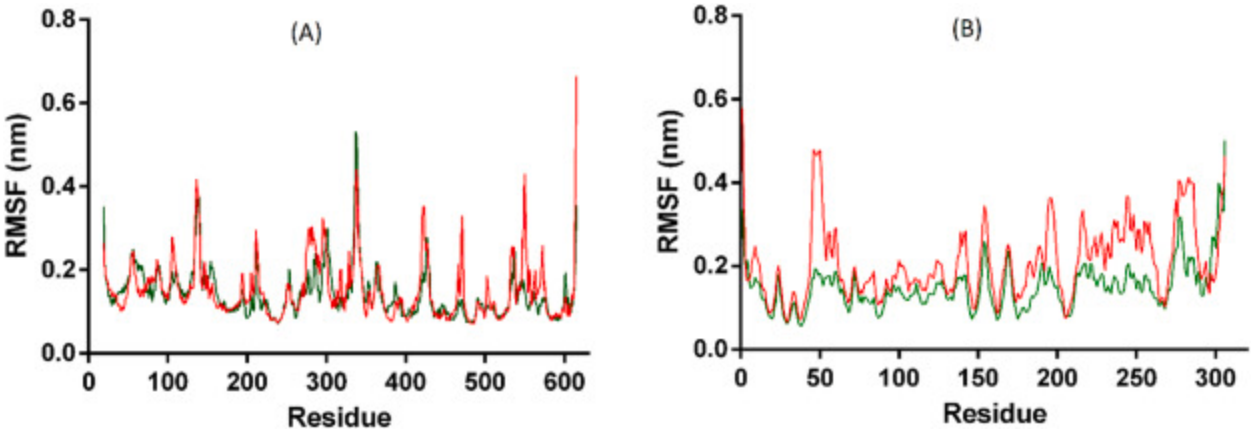

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Fig. 7. (A) and (B) displayed RMSF of ACE2 and M^{pro}.

In addition, the interface affinity of the protein and compound was analyzed by calculating the binding energy of the protein complex. The average binding energy calculated for ACE2 (BODO) and M^{pro}-(5GDE) complex is presented in Table 4 which represents that Van der Waals energy played a major role in maintaining the binding of compounds with protein in both of the complexes during the dynamics.

Table 4. The Binding energy of the protein-compound complex. Drug likeness property.

Complex	Van der Waal energy (Kj/mol)	Electrostatic energy (Kj/mol)	Polar salvation energy(Kj/mol)	SASA energy(Kj/mol)	Binding energy (Kj/mol)
ACE2-Comp	-181.67±0.97	-7.39±0.62	98.33±1.51	-15.75±0.08	-106.52±1.33
M^{pro}-Comp	-166.48±0.82	-40.96±0.65	108.23±0.89	-17.03±0.074	-116.31±0.89

Drug likeness is a crucial step in the initial step of drug discovery. The pharmacological properties of 4 high scoring phytochemicals of *A. adenophora* were studied. The pharmacokinetics profiling and toxicity predictions need to assess its drug-likeness property using Swiss ADME, which works on interpreting the molecular fingerprint of the submitted query structure, and analyze the presence or absence of chemical features in a molecule to publish pharmacokinetic data. The *in silico* pharmacokinetic predictions of the top 10 compounds of *A. adenophora* are depicted in Table 5.

Table 5. In silico pharmacokinetics prediction (Lipinski parameters) for the top 4 phytochemicals of *A. adenophora*.

Pharmacological properties	***BODO***	***5GDE***	***MDCQ***	***MDPC***
MW	504.61	382.40	532.49	516.49
n-rotb	1	4	11	10
n-HbA	6	8	12	11
n-HbD	0	4	6	6
ILog P	3.12	2.45	2.92	2.39
Lipinski violations	1	0	3	3
Lead likeness violations	1	1	2	2

MW: Molecular Weight, n-rotb: Number of rotable bonds, n-HbA: Number of hydrogen bond acceptor, n-HbD: Number of hydrogen bond donors.

Four compounds depicted in the table are high scoring compounds in 2 different receptors ACE2 and M^{pro} but BODO and 5GDE are the top-scoring compounds, respectively. These compounds also have single lead likeness violations. Therefore, these molecules can be considered for the further drug development steps. Among these two 5GDE has a molecular weight less than 500, which follow Lipinski's rule of five. This can propound that the compounds are safer and permissible for further study. The computational activity predication for expressed that selected phyto-compounds have mild to moderate potency against COVID-19 proteins.

3.3. Probable mechanism of action

The coronavirus is positive-strand RNA viruses (Weiss and Navas-Martin 2005). The process of viral replication and transcription is controlled by two overlapping polyproteins, the pp1a (replicase 1a, 450KD) and pp1ab (replicase 1ab, 750KD) (Yang et al., 2003). Frame shifting of the ribosome is essential for the expression of the C-proximal of pp1ab polyprotein (Kjær and Belsham 2018). The release of functional polypeptides from both polyproteins is controlled by M^{pro}, and necessary for proteolytic processing of polyproteins translated from viral RNA. The main protease slices the polyprotein by autolytic cleavage of the enzymes. This indicates blocking the activity of the main proteases could lead to inhibition of viral replication 5GDE, inhibits the M^{pro} with more binding affinity than native inhibitor through the multiple types of interactions.

Coronavirus also presents on protein S a specific binding site for ACE2 which serves as an entry point into the host cell. Various researches on ACE2 suggest, blocking the ACE2 receptor could make it more difficult for coronavirus to enter cells. BODO binds to the ACE2 receptor more effectively with higher binding affinity and most of the amino acid residue (GLU A:495, ASP A:494, PRO A:492, HIS A:493, TRP A:478, TYR A:613, GLUA:489) matches with native inhibitor hydroxychloroquine. 5GDE and BODO are phytochemicals of *A. adenophora* inhibit the viral replication and block the entry of SARS-CoV-2 through M^{pro} and ACE2 receptors. Phytochemicals of these two *A. adenophora* phytochemicals have shown more effective binding energy than its native inhibitors remdesivir and hydroxychloroquine.

4. Conclusion

Our aim of the study was to investigate efficiency of the phytocompounds against coronavirus. Therefore, the phytochemicals of *A. adenophora* are *in-silico* tested against M^{pro} and ACE2 receptor. Furthermore, the docking calculation confirmed that the phytocompound 5GDE consist significant identical interaction with selected protein as referenced compounds. However, the binding energy was measure slightly above than standard drug remdisivir and hydroxychloroquine. The MD analysis of M^{pro} complex structure found to retain similar compactness like its apo structure, but with increased structural stability and low residues fluctuation in comparison to the apo form during the simulation. Whereas, phytochemical BODO has shown high binding affinity (score), almost stable interaction with ACE2 receptor, retain similar compactness, and residues motion like its apo structure, but with increased structural stability during the simulation.

Our study showed natural compounds from *A. adenophora* have either similar or greater binding affinity than that of natural inhibitor remdesivir and hydroxychloroquine. Hence, 5GDE and BODO can be further developed as drug candidates against M^{pro} and ACE2 receptor of coronavirus, responsible for ongoing pandemic. Finally, we suggest from this *in-silico* study that *A. adenophora* phytochemicals block both M^{pro} and ACE2 receptors.

Declaration of competing interest

Authors have no conflict of interest regarding this article.

Acknowledgements

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…The host nuclear import system can be bound and sequestered by pathogens such as SARS-CoV-2 allowing transportation of viral proteins to the host nucleus leading to increased viral replication [25–29]. Additionally, we also consider the multi-functional helicase (nsp13) of SARS-CoV-2 responsible for viral replication (PDB: 6ZSL) [30–32], and the main protease (Mpro) of SARS-CoV-2 (PDB: 6LU7) as it is a key enzyme of coronaviruses and has a fundamental role in mediating viral replication and transcription, making it an attractive target for drugs [33–37]. All structures were obtained in PDB format from the RCSB Protein Data Bank (https://www.rcsb.org/)….

Show abstract

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1 Both the authors have equally contributed to the manuscript.

View Abstract

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SYNTHESIS, CHARACTERIZATION AND IN VITRO ANTIFUNGAL EVALUATION OF TRANSITION METAL COMPLEXES DERIVED FROM *N′*-SUBSTITUTED-4-METHYLPIPERIDINE-1-CARBOTHIOHYDRAZIDES

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ABSTRACT

Series of coordination complexes of Cr(III), Ni(II) and Zn(II) with various *N′*-substituted-4-methylpiperidine-1-carbothiohydrazides (**6a-f**) have been synthesized and characterized quantitatively and qualitatively by UV-visible spectroscopy, FTIR spectroscopy, ^{1}H NMR studies; microelemental analysis; electrical conductance values and magnetic susceptibility measurements. The metal complexes displayed greater antifungal activity than corresponding ligands and the order of their activity was found as [M(salmpth)(Py)] > [M(fmpth)$_2$] > [M(talmpth)$_2$]. The greater antifungal activity of metal complexes was found due to decrease in polarity of metal ions while coordinating with ligands during chelation process. The algacidal effect of few ligands *viz*. H_2salmpth, Hfmpth and Htalmpth and its chromium(III) complexes were also studied.

Keywords: Synthesis, Transition Metal Complexes, N'-Substituted-4-methylpiperidine-1-carbothiohydrazides, Antifungal Activity, Algacidal Effect.

INTRODUCTION

Modern coordination chemistry involves various types of strategically designed and functionalized ligand systems. Among them, *N′*-substituted-4-methylpiperidine-1-carbothiohydrazides are a salient class of Schiff base ligands in coordination chemistry due to the dual coordinating sites (N and S) as potential donors.[1-5] Moreover, the coordination compounds of transition metal ions with bidentate ligands having N and S as donor sites are considered significant due to similarity with redox-active metalloenzymes.[6-10] Furthermore, the potential of Schiff base ligands has urged the researchers to undertake them as an elite ligand.[11,12]

The synthesis of Schiff base ligands and their corresponding metal complexes in a controlled manner becomes an important strategic pathway.[13-16] In this study, we chose readily available, low-cost and potential organic molecules as precursors to synthesize the new Schiff base ligands and their metal complexes. The unique advantage of these Schiff base ligands is the change in their ligation behavior depending on the metallic systems and the stoichiometry.[17,18] Therefore given above said advantages, we had synthesized, characterized the novel Schiff base ligands (*N′*-Substituted-4-methylpiperidine-1-carbothiohydrazides, (6a-f) and their corresponding complexes of Cr(III), Ni(II) and Zn(II) (7a-z). These Schiff base ligands (6a-f) and potential metal complexes were subjected to antifungal evaluation and algicidal effect.

EXPERIMENTAL

Materials and Methods

The chemicals and solvents were procured from Sigma-Aldrich, USA and Merck KGaA, Darmstadt, Germany and employed without any purification.

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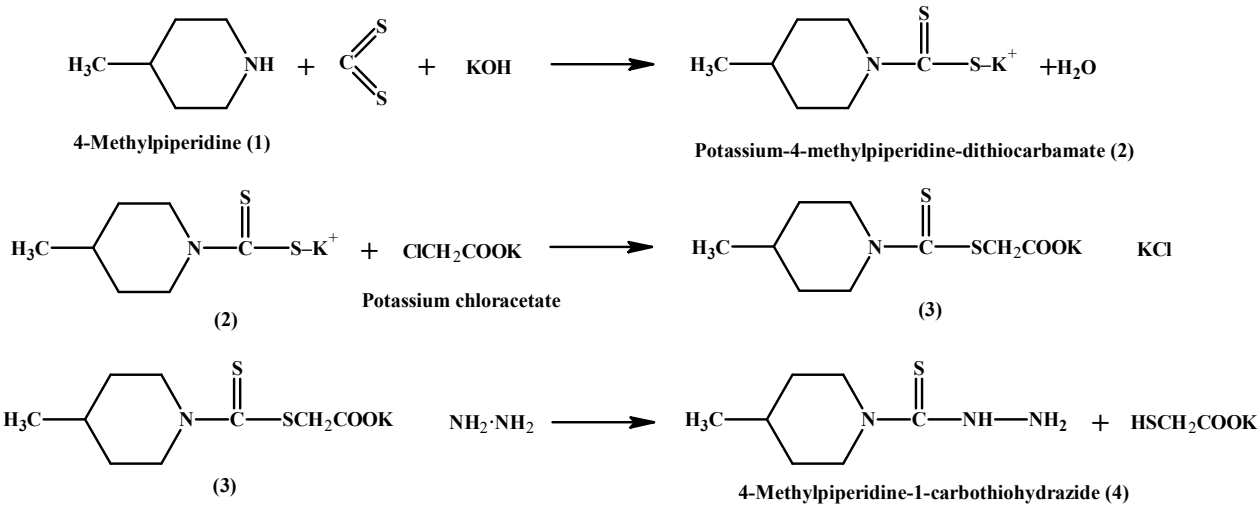
Characterization

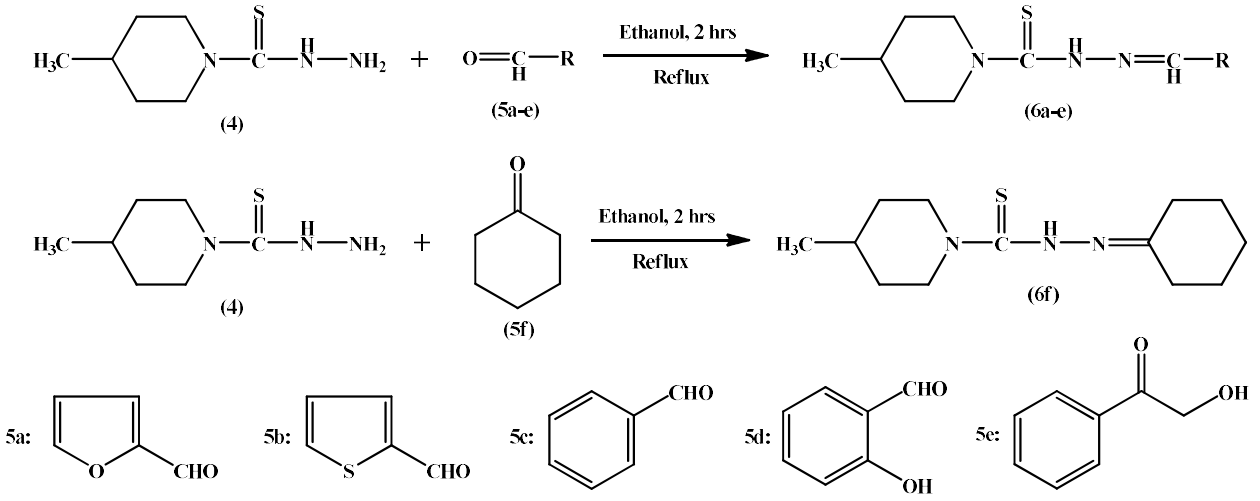
Gouy's method was used to determine the magnetic susceptibility at room temperature. FTIR spectra were recorded in the form of KBr disc between 4000-400 cm^{-1} on Perkin-Elmer FTIR spectrophotometer. The electronic absorption spectra of complexes and ligands were recorded between 200-900 nm in ethanol or DMF. ^1H NMR spectra were obtained on Bruker 400 MHz NMR Spectrometer using TMS as an internal standard. Sulphur and halogen were estimated gravimetrically in the form of $BaSO_4$ and AgCl, respectively. The metal ions were estimated by standard methods.[19]

Synthesis of Ligands

4-Methylpiperidine-1-carbothiohydrazide (4) was synthesized using the reported method[20,21] with few alterations (Scheme-I). The *N*′-Substituted-4-methylpiperidine-1-carbothiohydrazides (6a-f) were synthesized by refluxing an equimolar amount of 4-Methylpiperidine-1-carbothiohydrazide (4) and corresponding aldehyde/ketone (5a-f) in ethanol for 2 hours. On cooling, the resultant obtained was filtered, washed with cold ethanol and recrystallized from ethanol (Scheme-II). The physicochemical and analytical data of synthesized ligands (6a-f) are summarized in Table-1.



Scheme-I: Synthesis of 4-Methylpiperidine-1-carbothiohydrazide (4)



Scheme-II: Synthesis of *N*′-Substituted-4-methylpiperidine-1-carbothiohydrazides (6a-f)

Table-1: Physico-analytical Data of Synthesized Ligands (6a-f)

Ligands	Color	Melting Point (ºC)	Elemental Analysis: % Found (Calcd.)			
			C	H	N	S
4-Methylpiperidine-1-carbothiohydrazide (Hmpth, 4)	Flaky white	100	48.46 (48.55)	8.56 (8.67)	24.13 (24.27)	18.38 (18.49)
N′-cyclohexylidene-4-methylpiperidine-1-carbothiohydrazide (Hcycmpth, 6f)	Cream	149	61.47 (61.66)	10.48 (10.67)	16.44 (16.60)	12.32 (12.21)
N′-[(furan-2-yl)methylidene]-4-methylpiperidine-1-carbothiohydrazide (Hfmpth, 6a)	Cream	164	57.15 (57.37)	6.53 (6.77)	16.46 (16.73)	12.51 (12.74)
4-methyl-*N′*-[(thiophen-2-yl)methylidene]piperidine-1-carbothiohydrazide (Htalmpth, 6b)	Cream	169	53.68 (53.93)	6.18 (6.36)	15.50 (15.73)	23.73 (23.97)
N′-benzylidene-4-methylpiperidine-1-carbothiohydrazide (Hbenmpth, 6c)	Cream	143	64.11 (64.36)	7.08 (7.27)	15.83 (15.49)	11.92 (11.86)
N′-[(2-hydroxyphenyl)methylidene]-4-methylpiperidine-1-carbothiohydrazide (H2Salmpth, 6d)	White	158	60.48 (60.64)	6.62 (6.85)	14.95 (14.76)	11.31 (11.15)
N′-(2-hydroxy-1-phenylethylidene)-4-methylpiperidine-1-carbothiohydrazide (H2apmpth, 6e)	White	166	61.62 (61.85)	6.92 (6.81)	14.22 (14.43)	10.73 (10.99)

Synthesis of Metal Complexes

Chromium Complexes $[CrL(H_2O)_2Cl_2]$ (LH=Hcycmpth, Hfmpth, Htalmpth, Hbenmpth,) and $[CrL(H_2O)_2Cl]$ (LH_2=H_2salmpth, H_2apmpth)

An ethanolic solution of metal chloride ($CrCl_3 \cdot 6H_2O$, 40-50 mL) was added an ethanolic solution of respective ligands (molar ratio - 1:1) and the reaction mixture was refluxed for 3-4 hours. The pH was maintained at ≈7-8 by adding sodium acetate solution. On cooling, the resultant metal complexes were filtered, washed with ethanol and dried over $CaCl_2$ (anhydrous) at room temperature.

Nickel and Zinc Metal Complexes

(a) $[ML_2]$ (M=Ni^{2+} or Zn^{2+}; LH = Hcycmpth, Hfmpth, Htalmpth, Hbenmpth) and $[M(LH)_2]$ (M = Ni^{2+} or Zn^{2+}, LH_2 = H_2salmpth, H_2apmpth)

To an ethanolic/aqueous solution of metal chloride ($NiCl_2 \cdot 6H_2O$/ $ZnCl_2 \cdot H_2O$, 40-50 mL) was added hot ethanolic solution of appropriate ligand (1:2) slowly with continuous stirring and refluxed for 1-2 hours. On cooling, metal complexes were separated gradually. In the case of Zn(II) complexes, the complexes separated on adding an equal volume of water. The products were collected on a filter paper, washed with aqueous ethanol and dried over anhydrous $CaCl_2$ and finally vacuum dried.

$[ML(NH_3)]$ (M=Ni^{2+} or Zn^{2+}; LH_2= H_2salmpth, H_2apmpth)

An aqueous solution of appropriate metal acetate [$Ni(OAc)_2 \cdot 4H_2O$; $Zn(OAc)_2 \cdot 2H_2O$, 40-50 mL] was allowed to reflux for 2 hours with 40-50 mL ethanolic solution of appropriate ligand (1:1) in the presence of 15% of NH_4OH and pH was maintained at ≈ 9. The resulting metal complexes were collected on a filter paper, washed with aqueous ethanol and dried over anhydrous $CaCl_2$ and finally vacuum dried.

[ML(Py)] (M=Ni^{2+} or Zn^{2+}; LH_2= H_2salmpth, H_2apmpth)

An aqueous solution of metal chloride (0.0015 mol, 50 mL) was treated with 3-4 mL of pyridine and the resultant solution was added in hot ethanolic solution (50 mL) of appropriate ligand (0.0015 mol) and refluxed for 1-2 hours. On cooling, the metal complexes were separated. The solid product was washed with aqueous ethanol and dried with KOH+$CaCl_2$. Physico-analytical data of the synthesized complexes are given in Table-2.

Table-2: Physico-analytical Data of Schiff Base Metal Complexes derived from *N'*-substituted-4-methylpiperidine-1-carbothiohydrazides (6a-f)

Complexes	Color	Elemental Analysis: % Found (Calc.)					μeff (B.M.)	Λ_M (ohm^{-1} cm^2 mol^{-1})
		M	C	H	N	S		
$[Cr(cycmpth)(H_2O)_2Cl_2]$,7a	Green	12.47 (12.68)	37.94 (37.81)	5.92 (5.89)	10.11 (10.24)	7.95 (7.80)	3.87	5.71
$[Cr(fmpth)(H_2O)_2Cl_2]$, 7b	Dark green	12.50 (12.71)	34.88 (34.73)	4.69 (4.88)	10.11 (10.26)	7.66 (7.82)	3.90	8.33
$[Cr(talmpth)(H_2O)_2Cl_2]$, 7c	Dark Green	12.08 (12.23)	33.67 (33.88)	4.52 (4.70)	9.68 (9.88)	14.88 (14.95)	3.89	7.15
$[Cr(benmpth)(H_2O)_2Cl_2]$, 7d	Dark Green	12.18 (12.38)	39.90 (39.80)	5.28 (5.17)	9.73 (9.62)	7.42 (7.61)	3.88	6.29
$[Cr(salmpth)(H_2O)_2Cl]$, 7e	Brown	12.73 (12.98)	41.76 (41.94)	5.53 (5.34)	10.31 (10.44)	7.76 (7.69)	3.89	7.74
$[Cr(apmpth)(H_2O)_2Cl]$, 7f	Brown	12.32 (12.54)	43.22 (43.12)	5.83 (5.73)	9.97 (9.83)	7.53 (7.72)	3.90	7.37
$[Ni(cycmpth)_2]$, 7g	Brown	10.46 (10.51)	55.40 (55.61)	7.23 (7.48)	14.75 (14.97)	11.18 (11.40)	Diamag.	6.53
$[Zn(cycmpth)_2]$, 7h	Light Yellow	11.25 (11.46)	54.88 (54.72)	7.26 (7.40)	14.65 (14.81)	11.11 (11.28)	Diamag.	5.74
$[Ni(fmpth)_2]$, 7i	Brown	10.38 (10.55)	51.33 (51.52)	5.57 (5.72)	14.88 15.02	11.26 (11.44)	Diamag.	7.45
$[Zn(fmpth)_2]$, 7j	Yellow	11.31 (11.50)	50.73 (50.97)	5.48 (5.66)	14.94 (14.86)	11.20 (11.32)	Diamag.	8.92
$[Ni(talmpth)_2]$, 7k	Brown	9.77 (9.98)	48.55 (48.73)	5.24 (5.41)	14.05 (14.21)	21.44 (21.65)	Diamag.	6.28
$[Zn(talmpth)_2]$, 7l	Yellow	10.63 (10.88)	48.11 (48.24)	5.17 (5.36)	14.15 (14.07)	21.30 (21.44)	Diamag.	7.54
$[Ni(benmpth)_2]$, 7m	Orange Red	10.08 (10.22)	58.06 (58.23)	5.71 (5.89)	14.32 (14.55)	10.86 (10.79)	Diamag.	4.90
$[Zn(benmpth)_2]$, 7n	Orange Yellow	10.93 (11.04)	57.51 (57.63)	5.61 (5.83)	14.26 (14.10)	10.76 (10.67)	Diamag.	10.52
$[Ni(HSalmpth)_2]$, 7o	Reddish Brown	9.44 (9.68)	54.97 55.07	5.33 (5.58)	13.58 (13.79)	10.32 (10.50)	Diamag.	6.4
$[Zn(HSalmpth)_2]$, 7p	Yellow	10.32 (10.56)	55.25 (55.63)	5.26 (5.52)	13.48 (13.65)	10.27 (10.40)	Diamag.	7.36
$[Ni(Hapmpth)_2]$, 7q	Brick Red	9.12 (9.26)	56.28 (56.51)	5.64 (5.96)	12.93 (13.18)	9.88 (10.04)	Diamag.	6.50
$[Zn(Hapmpth)_2]$, 7r	Yellow	9.87 (10.01)	55.74 (55.98)	6.31 (6.53)	12.87 (12.76)	9.73 (9.65)	Diamag.	7.75
$[Ni(Salmpth)(NH_3)]$, 7s	Red	16.63 (16.80)	47.67 (47.86)	5.48 (5.69)	15.74 (15.65)	8.96 (8.91)	Diamag.	9.63
$[Zn(Salmpth)(NH_3)]$, 7t	Yellow	18.03 (18.20)	47.86 (47.05)	5.47 (5.60)	15.47 (15.68)	8.68 (8.96)	Diamag.	11.31
$[Ni(apmpth)(NH_3)]$, 7u	Reddish Brown	15.98 (16.06)	49.14 (49.31)	5.93 (6.02)	15.17 (15.34)	8.58 (8.46)	Diamag.	10.85
$[Zn(apmpth)(NH_3)]$, 7v	Yellow	17.37 (17.52)	48.36 (48.51)	5.68 (5.92)	14.92 (14.99)	8.47 (8.62)	Diamag.	11.26
[Ni(Salmpth)Py], 7w	Red	14.11 (14.28)	54.98 (55.02)	5.11 (5.32)	13.34 (13.55)	7.51 (7.74)	Diamag.	8.28
[Ni(apmpth)Py], 7x	Reddish Brown	13.62 (13.81)	56.03 (56.20)	5.41 (5.62)	12.92 (13.01)	7.23 (7.49)	Diamag.	9.57
[Zn(Salmpth)Py], 7y	Light Yellow	15.33 (15.51)	54.24 (54.41)	5.09 (5.25)	13.12 (13.36)	7.45 (7.63)	Diamag.	10.12
[Zn(apmpth)Py], 7z	Yellow	14.88 (14.71)	55.20 (55.42)	5.36 (5.54)	12.64 (12.93)	7.18 (7.11)	Diamag.	6.32

Table-3: Electronic Spectral Data of Schiff Base Metal Complexes derived from *N'*-substituted-4-methylpiperidine-1-carbothiohydrazides (6a-f)

Complexes	Electronic Bond Positions	Assingments
$[Cr(cycmpth)_2(H_2O)_2Cl_2]$	310w, 425s, 568sbr	$^4A_2g(F)\rightarrow{}^4T_{1g}(P)$; $^4A_{2g}(F)$-$^4T_{1g}(F)$; $^4A_{2g}(F)\rightarrow{}^4T_{2g}(P)$
$[Cr(fmpth)_2(H_2O)_2Cl_2]$	325w, 440sh, 580sbr	$^4A_2g(F)\rightarrow{}^4T_{1g}(P)$; $^4A_{2g}(F)$-$^4T_{1g}(F)$; $^4A_{2g}(F)\rightarrow{}^4T_{2g}(P)$
$[Cr(talmpth)_2(H_2O)_2Cl_2]$	315w, 432s, 570sbr	$^4A_2g(F)\rightarrow{}^4T_{1g}(P)$; $^4A_{2g}(F)$-$^4T_{1g}(F)$; $^4A_{2g}(F)\rightarrow{}^4T_{2g}(P)$
$[Cr(benmpth)_2(H_2O)_2Cl_2]$	318w, 445s, 575sbr	$^4A_2g(F)\rightarrow{}^4T_{1g}(P)$; $^4A_{2g}(F)$-$^4T_{1g}(F)$; $^4A_{2g}(F)\rightarrow{}^4T_{2g}(P)$
$[Cr(salmpth)(H_2O)_2Cl]$	320w, 452s, 582sbr	$^4A_2g(F)\rightarrow{}^4T_{1g}(P)$; $^4A_{2g}(F)$-$^4T_{1g}(F)$; $^4A_{2g}(F)\rightarrow{}^4T_{2g}(P)$
$[Cr(apmpth)(H_2O)_2Cl]$	325w, 455s, 585sbr	$^4A_2g(F)\rightarrow{}^4T_{1g}(P)$; $^4A_{2g}(F)$-$^4T_{1g}(F)$; $^4A_{2g}(F)\rightarrow{}^4T_{2g}(P)$
$[Ni(cycmpth)_2]$	290ms, 440sh	π-π^* ; $^1A_{1g}\rightarrow{}^1B_{1g}$
$[Ni(fmpth)_2]$	375sbr, 440br, 552m	C-T ; $A_{1g}\rightarrow{}^1B_{1g}$; $^1A_{1g}\rightarrow{}^1A_{2g}$
$[Ni(talmpth)_2]$	370sbr, 435br, 545m	C-T ; $^1A_{1g}\rightarrow{}^1B_{1g}$; $^1A_{1g}\rightarrow{}^1A_{2g}$
$[Ni(benmpth)_2]$	378br, 450m, 560m	C-T ; $^1A_{1g}\rightarrow{}^1B_{1g}$; $^1A_{1g}\rightarrow{}^1A_{2g}$
$[Ni(HSalmpth)_2]$	368b, 455mb, 565m	C-T ; $^1A_{1g}\rightarrow{}^1B_{1g}$; $^1A_{1g}\rightarrow{}^1A_{2g}$
$[Ni(Hapmpth)_2]$	272s, 370br, 460sh, 567m	π-π^* ; C-T; $^{1A}{}_{1g}\rightarrow{}^{1B}{}_{1g}$; $^1A_{1g}\rightarrow{}^1A_{2g}$
$[Ni(Salmpth)(NH_3)]$	262s, 370sbr, 450sh	π-π^* ;C-T ; $^1A_{1g}\rightarrow{}^1B_{1g}$
$[Ni(apmpth)(NH_3)]$	260s, 365sbr, 447sh	π-π^* ;C-T ; $^1A_{1g}\rightarrow{}^1B_{1g}$
[Ni(salmpth)(Py)	265s, 372sbr, 450sh	π-π^* ;C-T ; $^1A_{1g}\rightarrow{}^1B_{1g}$
[Ni(apmpth)(Py)	262s, 368sbr, 445sh	π-π^* ;C-T ; $^1A_{1g}\rightarrow{}^1B_{1g}$

(Sh = shoulder, m = medium, s= strong, sbr = strong and broad)

RESULTS AND DISCUSSION

The analytical data recorded in Table-2 were found fully consistent with the composition of the complexes synthesized. Thermogravimetric analysis shows that all the synthesized complexes are stable below 180-190 ºC. The complexes are lesser soluble in ordinary organic solvents and are much soluble in DMSO, DMF and dioxane. Molar conductance of all the complexes was found in the range 5-15 Ω^{-1} cm^2 mol^{-1} displaying their non-ionic nature.[22] The Cr(III) complexes have magnetic moments value between 3.87-3.91 B.M. indicating their octahedral geometry. The diamagnetism of all Ni(II) complexes indicates their square planar geometry[23]. The preference for tetrahedral stereochemistry for complexes of d^{10} electronic system and observed metal-ligand stoichiometry indicate the tetrahedral structure for Zn(II) complexes, which were established as diamagnetic.[24]

Electronic Spectral Studies

The chemical spectra of all Cr(III) complexes were obtained in DMSO. The complexes exhibited bands at 16806-18518 cm^{-1} (595-540 nm), 22831-23539 cm^{-1} (438-425 nm) and 31250-32573 cm^{-1} (320-307 nm) which may be assigned to ^4A_2g (F) $\rightarrow$ ^4T_2g (F) (ν_1), $^4A_2g(F)\rightarrow{}^4T_1g(F)$ (ν_2) and ^4A_2g (F) $\rightarrow$ ^4T_1g (P) (ν_3) transitions sequentially in order of increasing energy. Out of these three spin-allowed *d-d* transitions, the one of lowest energy is a direct measure of the crystal field splitting Δ or 10Dq. These values are in better compliance with the reported values for octahedral Cr(III) complexes[25, 26]. The solid reflectance spectra of Ni(II) complexes below 400 nm display strong absorptions attributed to charge transfer band or ligand absorptions. A weak band or shoulder in the region 420-480 nm and 500-600 nm are attributed to $^1A_1g\rightarrow{}^1B_1g$ and $^1A_1g\rightarrow{}^1A_2g$ transitions respectively in a planner arrangement of Ni(II) atom geometry[23]. The broadband of thioamide ligands was observed in the regions $\approx$ 365 nm and suffered a blue shift in the complexes due to thioenolization, which broadens considerably due to overlap of ligands to metal charge transfer transitions[27] (Table-3).

FTIR Spectral Studies

The IR spectra of ligands exhibited bands at 1625 ± 5 cm^{-1}, which is due to $\nu_{C=N}$ of the azomethine group. The same band is observed at a lower frequency by 15-10 cm^{-1} as a strong band in all the complexes of Cr(III), Ni(II) and Zn(II) attributed to the coordination through azomethine nitrogen. It is further confirmed by the appearance of azine chromophore (>C=N-N=C<) around 1605-1600 cm^{-1} in the

complexes. The characteristic phenolic $\nu_{(O-H)}$ band due to the presence of -OH group at ortho position of ligands (H_2Salmpth) and (H_2ampth) was observed at 3293-3180 cm^{-1}, disappeared in the monoligated complexes of Cr(III), Ni(II) and Zn(II) having compositions [$CrL(H_2O)_2Cl$], [ML(Py)], [$ML(NH_3)$] (M=Ni^{2+} or Zn^{2+}, LH_2=H_2Salmpth, H_2apmth) suggesting the coordination by the phenolic oxygen after deprotonation. This broadband is intact in bischelates of Ni(II) and Zn(II) having compositions [ML_2] and [$M(LH_2)$ (LH=Hcycmpth, Hfmpth,Htalmpth, Hbenmpth and LH_2= H_2Salmpth, H_2ampth) and attributed to uncoordinated –OH and involved in H-bonding. In all the aqua complexes of Cr(III) having composition [$ML(H_2O)$] (LH_2= H_2Salmpth, H_2apampth) a broad bond appeared in the range of 3400-3300 cm^{-1} showing the existence of water. The rocking band of H_2O is not observed for coordinated water which indicates the lattice nature of H_2O in the complexes.[28] Drastic conditions required to dehydrate these complexes also confirm a structure containing water molecules in these complexes. The absence of any band in the region of 2600-2500 cm^{-1} due to $\nu_{(SH)}$ shows that all the ligands exist in thio-keto form, which is also supported by ^{1}H NMR studies. The IR absorption bands of ν_{NH} in the region 3300-3100 cm^{-1} of the free ligands disappeared in all the complexes indicating that the ligands are deprotonated in the complexes. The thioamide bands (IV) of the free ligands (935-865 cm^{-1}) which have a major contribution from $\nu_{c=s}$ vibration is observed at 705 ± 20 cm^{-1} in all the complexes, showing the coordination with deprotonated thiol sulphur. The coordination of NH_3 in the complex [$ML(NH_3)$)] [M=Ni^{2+} or Zn^{2+}, LH_2= H_2Salmpth, H_2apmpth] is indicated by the appearance of bands at 3300-3100, 1590, 1280 and 850 cm^{-1} assigned to νNH_3, δNH_3, ρNH_3 sequentially. The pyridine ring breathing mode of vibration observed at 1025 ± 5 cm^{-1} is regarded as a coordinated pyridine molecule.[29] The $\nu_{C=N}$ for such complexes was observed at 1595 ± 5 cm^{-1}. In the far-infrared region, all the complexes displayed several bands at 460-410, 400-380, 360-320 and 300-230 cm^{-1} those are assigned to M–O, M–N, M–S, M–Cl *str* vibration, respectively.

It was observed that in slightly alkaline conditions pH≈7-8 (or 9), the ligands H_2Salmpth and H_2apmpth, react with Cr(III), Ni(II) or Zn(II) salts giving rise to monoligated complexes [$CrL(H_2O)_2Cl$], [ML(Py)] and [$ML(NH_3)$], (M = Ni^{2+} or Zn^{2+}). It behaves in a dibasic tridentate manner and bonding takes place through O, N and S. In feebly alkaline or neutral conditions these and other ligands are found to act in a bidentate monobasic way bonding through azomethine N-atom and S-atom (*via* thioenolisation) keeping the –OH free.

^{1}H NMR Studies

The signals due to –NH proton at δ ≈11.8 ppm and phenolic –OH at δ ≈12.4-13.04 ppm of ligands H_2Salmpth and H_2apmpth disappeared in its monoligated complexes of compositions [$CrL(H_2O)_2Cl$], [ML(Py)] and [$ML(NH_3)$], (M = Ni^{2+} or Zn^{2+}), which shows the diabasic tridentate nature of these ligands in the complexes and bonding through O, N and S atoms. In the neutral bischelates of Ni(II) and Zn(II) signals due to –NH proton at δ 11-12 ppm of ligands disappears in complexes suggesting the thioenolization and coordination through deprotonated thiol sulphur atoms. In neutral, bischelates of H_2Salmpth and H_2apmpth of Ni(II) and Zn(II) the signals due to phenolic –OH at ≈12.4-13.04 ppm remain unaffected in complexes and its downfield shift than normal phenolic –OH shows H–bonding. The chemical shift δ 7.1-7.3 ppm of aromatic protons undergoes a slight downfield shift δ 7.4-7.9 ppm on complexation.

Thus, based on the above studies, the following tentative structures (Fig. 1.) have been proposed for the synthesized complexes.

Antifungal Evaluation

4-Methylpiperidine-1-carbothiohydrazide (4), *N′*-substituted-4-methylpiperidine-1-carbothiohydrazides (6a-f), monoligated pyridine complexes of *N′*-substituted-4-methylpiperidine-1-carbothiohydrazides derived from salicylaldehyde [M(salmpth)(Py)] and bis-ligated complexes derived from furfural [$M(fmpth)_2$] and thiophene-2-aldehyde [$M(talmpth)_2$], (M=Ni^{2+} or Zn^{2+}) have been tested for antifungal activity. Antifungal activity of these compounds was evaluated by Agar-based disk-diffusion method[30] against fungal strains *C. albicans* and *A. niger* using Griseofulvin as a standard drug. The results are

shown in Table-4. All the tested compounds were found to possess moderate to significant antifungal activity. The complexes were found more active than ligands and the order of their activity was found as $[M(salmpth)(Py)] > [M(fmpth)_2] > [M(talmpth)_2]$.

The algacidal effect of $CrCl_3$, the ligands- H_2salmpth, Hfmpth and Htalmpth and their chromium complexes were studied on the growth of green algae- chlorella. The ligands and complexes were found less toxic than metal chloride. The lesser algacidal effect of ligands and complexes concerning metal ions may be attributed to their larger size.

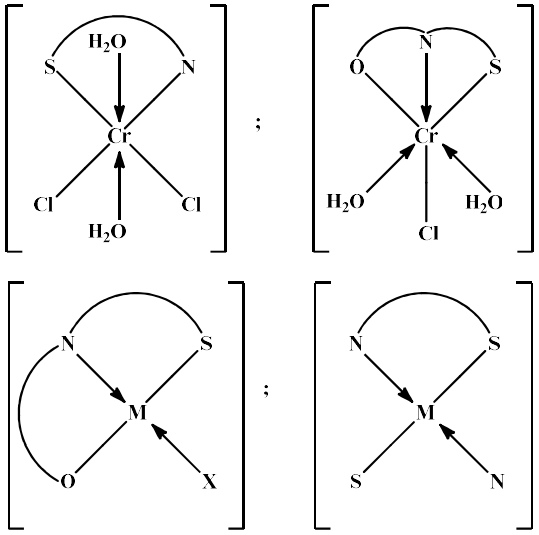


Fig. -1: Tentative Structures of the Complexes synthesized. Where X= Py or NH_3; M= Ni^{2+} or Zn^{2+}. The parts involving O, N and S atoms in the above structures represent the donor system of the ligands

Table-4: Antifungal Activity of 4-Methylpiperidine-1-carbothiohydrazide (4), *N*′-Substituted-4-methylpiperidine-1-carbothiohydrazides (6a-f) and Schiff base metal complexes (7w, 7y, 7i, 7j, 7k, 7l)

Tested Compound at a Concentration of 100 µg/ml	Zone of Inhibition (in mm)	
	C. albicans	*A. niger*
Hmpth, 4	08	10
Hfmpth, 6a	10	12
Htalmpth, 6b	09	10
Hbenmpth, 6c	05	-
H_2Salmpth, 6d	12	10
(H_2apmpth, 6e	08	11
Hcycmpth, 6f	12	10
[Ni(Salmpth)Py], 7w	17	19
[Zn(Salmpth)Py], 7y	19	20
$[Ni(fmpth)_2]$, 7i	14	11
$[Zn(fmpth)_2]$, 7j	15	14
$[Ni(talmpth)_2]$, 7k	12	10
$[Zn(talmpth)_2]$, 7l	14	10
Griseofulvin	22	25

CONCLUSION

Three bidentate N, S donor type *N*′-Substituted-4-methylpiperidine-1-carbothiohydrazides (**6a-f**) were synthesized using cyclohexanone, thiophene-2-aldehyde, benzaldehyde, salicylaldehyde, furfural and 2-hydroxyacetophenone. These ligands were complexed with transition metals to produce their metal complexes. Physico-analytical data including spectral data and elemental analysis of ligands & their metal(II) complexes were shown as per proposed structures. Potential ligands & their metal complexes

were tested for antifungal and algacidal potential. Results showed that metal complexes have greater antifungal activity in comparison to corresponding ligands. The greater antifungal activity of metal complexes was shown due to the chelation phenomenon, which coordinates the metal ion with ligands and makes a reduction in its polarity.

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Naturally occurring heterocyclic anticancer compounds

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Abstract

Naturally occurring heterocyclic scaffolds are key ingredients for the development of various therapeutics employed for biomedical applications. Heterocyclic pharmacophores are widely disseminated and have been befallen in almost all categories of drugs for the alleviation of myriad ailments including diabetes, neurodegenerative, psychiatric, microbial infections, disastrous cancers etc. Countless fused heterocyclic anticancerous templates are reported to display antimetabolite, antioxidant, antiproliferative, cytostatic etc. pharmacological actions via targeting different signaling pathways (cell cycle, PI-3kinase/Akt, p53, caspase extrinsic pathway etc.), overexpressive receptors (EGRF, HER2, EGF, VEGF etc.) and physiological enzymes (topoisomerase I and II, cyclin dependent kinase etc.). A compiled description on various natural sources (plants, microbes, marine) containing anticancer agents comprising heterocyclic ring specified with presence of nitrogen (vincristine, vinblastine, indole-3-carbinol, meridianins, piperine, lamellarins etc.), oxygen (paclitaxel, halichondrin B, quercetin, myricetin, kaempferol etc.) and sulphur atoms (brugine, fucoidan, carrageenan etc.) are displayed here along with their molecular level cytotoxic action and therapeutic applications.

Keywords: antimetabolite; cytotoxic; heterocyclic scaffolds; overexpressive receptors; signal pathways

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Review

Polycystic ovarian syndrome: A review covering phytoconstituents for its outstrip management

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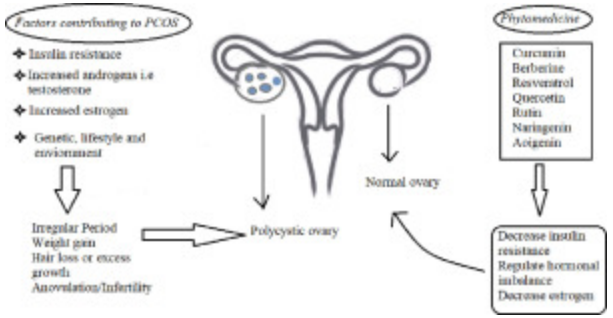
Abstract

Polycystic ovarian syndrome (PCOS) is a multifactorial disease affecting women of all age groups in reproductive age and post-menopausal women. It is associated with a large range of clinical manifestations. Medical treatment depends on the symptoms observed, and the most common symptoms addressed in the case of PCOS are infertility, hirsutism, menstrual disorders, and obesity. There are significantly fewer therapies that can work on many symptoms, and the most difficult one is to treat infertility and hirsutism together, leading to a very hectic, tedious, and frustrating therapeutic period for patients.

Current treatments are associated with severe side effects, including visual disturbance, hot flushes, abdominal distension, mood swings associated with clomiphene citrate, while polymenorrhagia with spironolactone. Thus, phytoconstituents and lifestyle modification can be considered as a safe and effective treatment approach for PCOS management as are free from serious adverse effects and can work out at multiple targets simultaneously. The research reports have demonstrated the fact that phytoconstituents like curcumin, resveratrol, and berberine have great potential in reducing insulin resistance, modulating L.H. to FSH ratio, and reducing metabolic syndromes associated with the disease. The results obtained revealed that these phytoconstituents have comparable results with first-line drugs such as clomiphene and metformin in improving fertility, reducing obesity, and regularizing the menstrual cycle. The present review covers the pathophysiology of PCOS, the current treatment approach and their drawbacks, detailed preclinical and clinical studies phytoconstituents that have proven potential in managing PCOS symptoms along with their regulatory aspects.

Graphical abstract



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Keywords

Polycystic ovarian syndrome; Phytoconstituents; Curcumin; Berberine; Resveratrol; Apigenin

1. Introduction

Polycystic ovarian syndrome (PCOS) is a multifactorial disease also called Stein– Leventhal syndrome or hyperandrogenic anovulation (H.A.). This disorder is one of the most common problems that affect women of all age groups in reproductive age and post-menopausal women and is associated with an extensive range of clinical manifestations [1]. The disease is characterized by severe fertility and reproductive health issues and can be potentially threatening when combines with other lifestyle-related disorders like obesity, metabolic disorders, or cardiovascular disorders. Stein and Leventhal in 1935, first described this disorder, and it is characterized by the presence of 10 or more small cysts underdeveloped ovarian follicles of the size of 2–9mm in single or both ovaries [2].

As per the National Institutes of Health (NIH), approximately 4 – 10% of females belonging to the age group of 18–45 years have suffered from the ill effects of this disease called PCOS [1]. In previous years when the information available was meager, it was only affecting adult women until recent evidence clearly proved that the disorder is a lifelong syndrome, manifesting since prenatal age. PCOS prevalence is traditionally estimated at 4%–8% from studies performed in Greece, Spain, and the USA [3]. According to the Rotterdam diagnostic criteria, it was reported that a prevalence rate of 3 to 26% is found in adolescents [4].

The disease affects physical and mental status and affects the economic well-being of the individual and carries an enormous economic burden. In the USA, approximately 4 billion dollars are spent every year to screen for the disease and manage various linked morbidities like obesity, hirsutism, diabetes mellitus, and infertility [5]. It was reported that the Australian Health annual budget of more than 800 million dollars is involved in diagnosing, mitigating, and management of this multifaceted disease [5]. The disease is associated with various co- morbidities if left untreated and if appropriate medical consultation is not taken. Thus, it is essential to have early diagnosis and treatment to prevent future health co-morbidities and reduce financial burden [6, 7].

The main factors which play a significant role in PCOS development include increased insulin level, hypothalamic-pituitary dysfunction, and ovarian dysfunction [6]. In PCOS, there is increased Luteinizing hormone (L.H.) to Follicle-stimulating hormone (FSH) secretion, further leading to increased secretion of ovarian androgens [8]. Increased levels of insulin work on the hypothalamus-pituitary gonad axis and stimulate L.H. to FSH ratio simultaneously enhance androgens synthesis. This results in excess testosterone, androstenedione, and dehydroepiandrosterone by the ovaries in the patients suffering from PCOS [6, 8].

Current treatment approaches utilized for PCOS management mainly include lifestyle modification, insulin sensitizer molecules, nutritional supplements, ovulation induction, high testosterone therapy, assisted reproductive technology therapy, and surgical treatment [9,10]. The primary treatment approach is based on decreasing insulin resistance and glucose intolerance which is mainly achieved by metformin [10,11]. However, recent studies also reported that pioglitazone could also be a potential therapeutic agent improving the menstrual cycle and ovulation of PCOS patients [12]. Hormonal Contraceptives are used as first line drugs in case of PCOS utilized for normalizing hormonal imbalances and reducing obesity and ovulatory dysfunctions. However, due to various side effects, there is a growing tendency to utilize herbal drugs and phytoconstituents. The main class of therapeutic agents used are natural antioxidants and anti-inflammatory agents to regulate metabolic disorders and hormonal imbalances and reduce associated severe co-morbidities like prolonged hypertension and hyperlipidaemia that may lead to Myocardial infarctions [12,13]. The phytoconstituents could be utilized as therapeutic agents in PCOS treatment in various ways starting from producing steroidogenic response and express estrogen receptor protein to the reduction of androgens, from increasing glucose uptake and to decreasing insulin resistance and improving metabolism [13,14].

These phytoconstituents are obtained from traditional Chinese herbs which has been used since ancient time and has now become a major part of China's medical system. Phytoconstituents as Conventional and alternative medicines (CAMS) are therefore a popular adjunct therapy in the treatment of PCOS as they are effective for female reproductive problems [15,16] and are generally associated with few side effects [17]. Traditional Chinese medicine formulas and herbs have been used to manage the health problems of women for hundreds of years. From ancient times, Chinese medicine prescription was composed of variety of herbs for treating specific diseases. Herbal formula and single herb were reportedly used by over 70% of women with PCOS and are a commonly encountered condition among traditional Chinese doctors . Many studies showed that both herbal formula and single herb are helpful for fertility, menstrual health, and other aspects of PCOS. In view of the

use of Herbal Medicine in PCOS are becoming popular in research and clinical practice [18]. Berberine (BBR) is one of the major components of the Chinese herbal medicines derived from Rhizoma Coptidis, Cortex Phellodendri, and Cortex Berberidis and has been utilized in treating diarrhea, metabolic disorders, and infertility for long time. It has been used for thousands of years in its herbal form to enhance fertility and recently as an extract combined with cyproterone acetate (CPA), clomiphene (CC), and letrozole (LET), to enhance their effectiveness. Recently, a large body of evidence has demonstrated that BBR has a comparable activity to Metformin in reducing IR [19], [20], [21], [22].

Curcuma and variety of herbal extracts have been used and can improve the menstrual cycle, ovulation, and fertility by regulating the secretion of endocrine hormones. The phytoconstituents present in the herbal extract may act directly on the hypothalamus to affect the hypothalamus-pituitary axis and reduce the release of gonadotrophin-releasing hormone, subsequently balancing the concentrations of LH, FSH, and T [23].

The reduction of LH levels results into increased sensitivity of ovarian tissue to circulating FSH, contributing to alleviation of the symptoms of excessive androgens, the follicular growth, and ovulation. Also, it was reported by various sources that many single herbs also have estrogen-like function, which was directly related to improve the implantation rate and pregnancy outcome, and can decrease the serum level of androgens by increasing the level of SHBG [24]. Resveratrol, a polyphenol which is the main constituent of the Chinese herb Hu Zhang (Polygoni Cuspidiati Rhizoma) has been observed to have antioxidant, anticancer and anti-inflammatory effects [25], [26], [27]. It was reported by various researchers and was proven clinically and experimentally that Resveratrol is highly effective in the treatment of PCOS as it has been suggested that the compound has antidiabetic effects [27]. In rat theca cells, resveratrol has been shown to inhibit cellular proliferation [28] and androgen production by a reduction in androstenedione levels and decrease in the expression of CYP17A mRNA [29]. Therefore, they may have important therapeutic potential for ovulatory dysfunction in PCOS

It has been reported by various research reports that ginsenosides derived from Ren Shen (Panax ginseng) possess antidiabetic qualities. Clinically, ginsenosides improve insulin sensitivity and glucose levels [30] in T2DM patients, an effect mirrored in diabetic rats, with evidence indicating improvements in both insulin and leptin sensitivity [26]. It was also reported by the help of rat model for PCOS that ginsenosides produced reproductive benefits as ginsenosides improved ovarian weight and reduced the number of antral follicles when compared to the model group [31].

So, it can be concluded that Chinese herbal medicines posses good clinical effectivity against PCOS and this single phytoconstituents can add up in increasing the efficacy and safety of the compounds.

This review will focus on the most recent information and research related to the etiology, the pathophysiology of the disease, diagnostic criteria, their limitations, treatment options prevailing, and phytoconstituents' role in mitigating and managing this complex disorder.

2. A basic understanding of PCOS

The symptoms, diagnostic criteria, and even the causes of PCOS development are a debatable issue until now, irrespective of certain workshops and joint conferences to reach a common conclusion. A joint suggestion by members of the European Society of Human Reproduction and Embryology and the American Society of Reproductive Medicine in 2003 — the so-called Rotterdam criteria - which was also unaccepted globally, and three definitions for PCOS remain on the present-day also.

The Rotterdam definition is the most widely used and has the widest acceptance [32], [33], [34], [35], [36], [37]. The definition gives a hypothesis that the presence of PCOS can only be confirmed having at least two of the three characteristics (a) clinical and/or biochemical increased level of androgen,

(b) anovulation, and (c) polycystic ovarian morphology. Despite various workshops and conferences, a standard definition is still lacking, and Table1 gives an insight into various diagnostic criteria as per different agencies and societies. However, as per “Androgen Excess and PCOS Society” (A.E.–PCOS), PCOS is said to be present in the case of women if there is the presence of hyperandrogenism along with ovarian dysfunction in the form of ovulatory dysfunction and/or PCOM1, [38,39]. Finally, the National Institute of Child Health and Human Development gives an older definition that requires the presence of both.

Table 1. Diagnostic criteria for PCOS.

Presentation	NIH, 1990	ESHRE/ASRM, 2003	AES, 2006
Clinical or biochemical hyperandrogenism	Present	Present	Present
Oligo/anovulation	Present	Present	Present

Presentation	NIH, 1990	ESHRE/ASRM, 2003	AES, 2006
Presence of multiple cysts		Present	Present

NIH: National Institute of Health of the United States.

ESHRE: European Society of Human Reproduction and Embryology.

ASRM: American Society of Reproductive Medicine; AES: Androgen Excess and PCOS Society.

*** NIH deals with only two parameters while ESHRE and AES evaluate 3 characteristics.

In case of ESHRE any two presentations out of three will be associated with PCOS.

In the case of AES, consideration is given to all the three criteria/presentations.

3. Etiology of PCOS: a multifaceted disorder

Despite continuous research in the field to better understand the morphology and pathology, and treatment approaches for PCOS, the primary cause of PCOS is still unknown. The most accepted model is that PCOS is a multifaceted disease involving various factors like genetics, environment, and intrinsic individual factors, which interact with leading to physiological consequences and, finally, a vicious hormonal and physiological cycle. The final factor in the disease progression is the development of hyperandrogenaemia, which leads to most of the clinical symptoms developed and is also the primary marker utilized for the diagnosis of PCOS. [40].

In PCOS, the ovarian cycle is disturbed at various levels. Anti-Mullerian Hormone (AMH), secreted by the granulosa cells, is a hormone present in high concentration in primordial antral follicles and controls the conversion of primordial follicles to primary stage follicles as a check factor [41]. Excessive secretion of the AMH hormone disrupts the normal cycle of the phenomenon of ovarian follicle development. It prevents the further development of follicles by inhibiting the response to FSH [42], finally leading to immature follicles that can cause infertility issues [43].

The second most common feature associated with PCOS is a disruption in the feedback system of the hypothalamus-hypophysis ovary axis (HHOA [44], which resulted in excess concentration of gonadotropin-releasing hormone (GnRH). Further, that results in an excess amount of luteinizing hormone (L.H.) to Follicle-stimulating hormone (FSH) secretions in the blood. This altered amount of the two hormones leads to excess production of androgen from the theca cells of the ovary. [45]. This further results in a decrease in the concentration of oestradiol and progesterone, which in turn again stimulates gonadotropic hypothalamic cells to secrete more amounts of GnRH and L.H. Thus this vicious cycle continues [46]. This plays the most crucial role in the development and progression of the disorder as shown in Fig.2. The excess androgens result in acne, hirsutism, co-morbidities like obesity and metabolic syndrome, etc., along with the development of immature multi follicles in the ovary termed PCOS. [47], which maintains all the characteristic hormonal imbalances.

The development of PCOS depends on certain Genetic factors as reported by various research reports that play an important role in developing this syndrome by helping in the production of abnormally high androgen in ovarian tissue. It is believed that PCOS follows Mendelian pattern of inheritance, in which the genetic defects pass to the next generation being a dominant autosomal allele, which is dependent on certain other factors including environmental conditions and epigenetic factors [48]. Sometimes, sudden inherent mutations in the genes coding for the androgen receptor, sex hormone-binding globulin (SHBG), and steroidogenic enzymes can be a factor in the development of hyperandrogenemia [49].

4. Clinical manifestations of PCOS

PCOS exhibition is significantly heterogeneous in the clinical setting, with an expansive clinical sign spectrum (Fig.1). Albeit the presence of oligomenorrhea demonstrates ovulatory brokenness, evident eumenorrhea does not totally preclude anovulation. The progesterone levels of < 3–4ng/mL in days 20–24 of the menstrual cycle are sufficient to evaluate the condition and result from being oligo/anovulatory. Conversely, a patient can be analyzed as anovulatory after learning anovulation in any event 2 menstrual cycles, within the sight of hypoprogesteronemia [50].

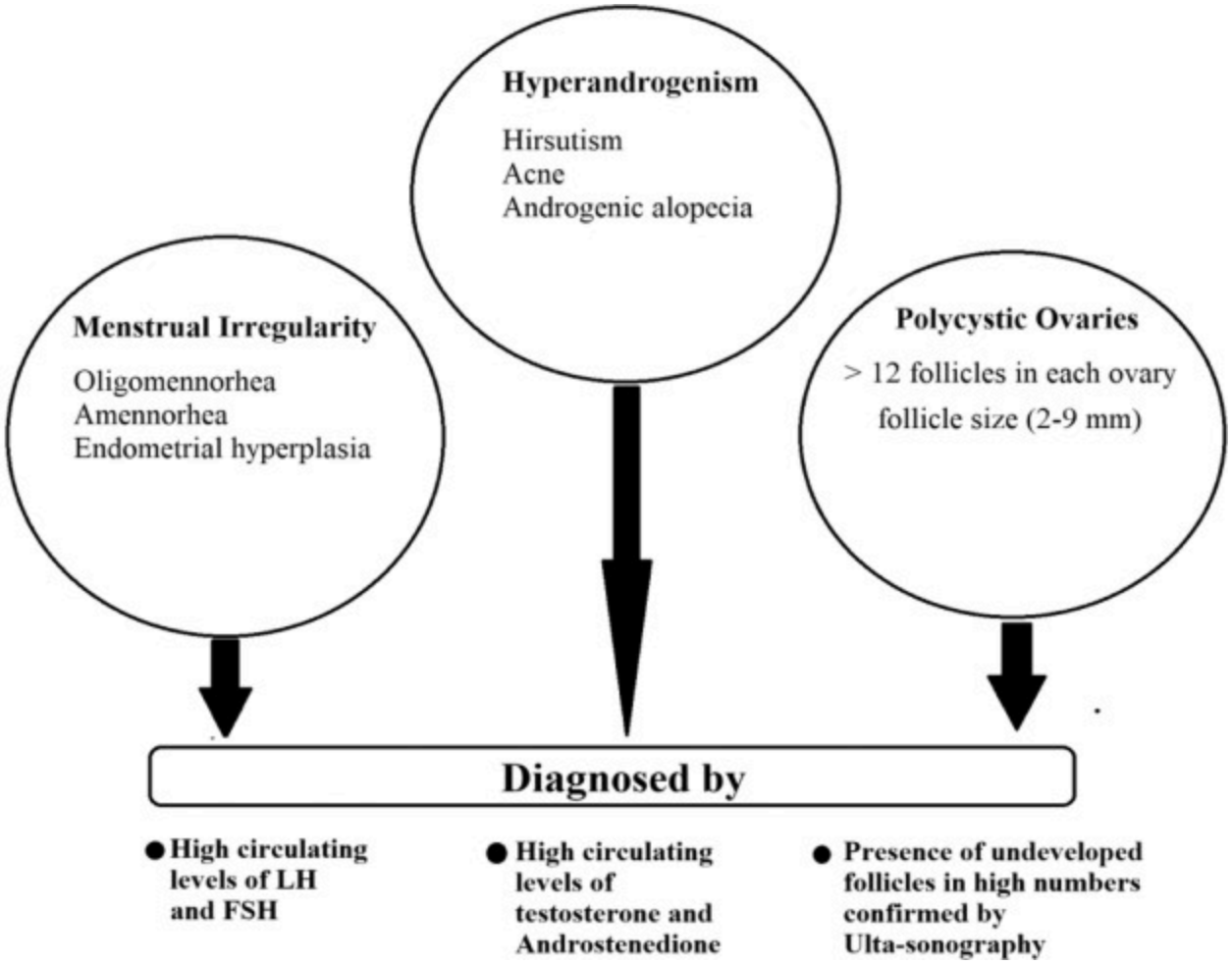

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Fig. 1. Clinical sign and symptoms of PCOS.

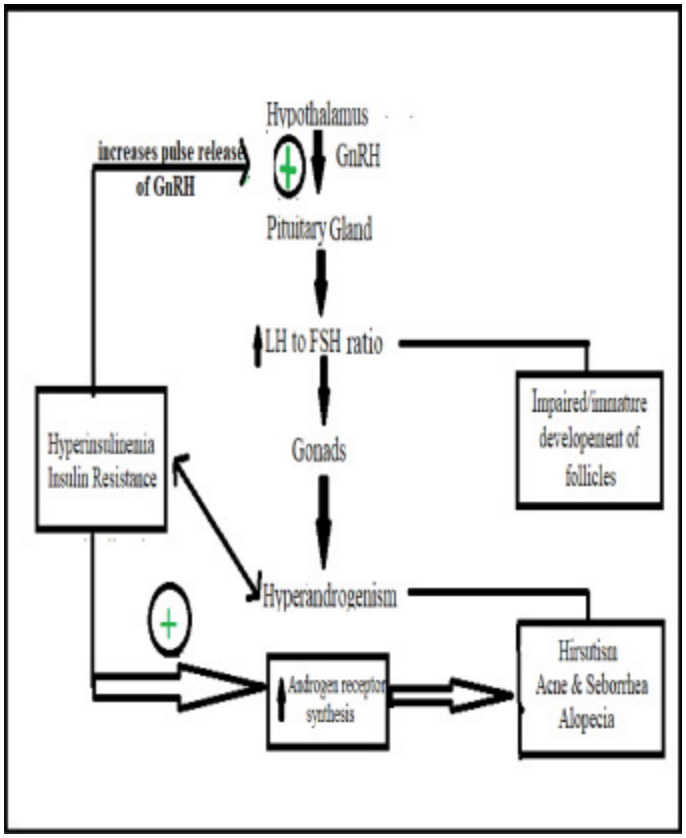

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Fig. 2. Proposed pathophysiology of PCOS.

4.1. Hirsutism

Hirsutism is the condition that results in excessive terminal hair in areas of the body that are usually hairless or with limited hair growth, such as the face, chest, areolas, abdomen, and upper thighs due to higher concentration of androgen. There are four different androgenic molecules secreted in a female reproductive age, including testosterone, dihydrotestosterone (DHT)

dehydroepiandrosterone sulfate (DHEAS), androstenedione. Only testosterone and DHT can bind to the androgen receptor and produce altered hair follicle morphology and physiology [51], [52], [53].

4.2. Acne and seborrhea

Sebaceous glands are small oil producing glands present in males and females both. The sebaceous glands are highly sensitive to the androgen concentration and release. The enhanced androgen concentration in case of PCOS leads to stimulation of sebaceous glands to produce more sebum, leading to the development of acne and seborrhoea [54]. The androgens are responsible for the proliferation of sebocytes mainly in forehead, chin and mid back region [55]. The local bacteria infect the hair follicle structure and release lipolytic enzymes, causing breakdown of triglycerides produced in the sebocyte, leading to blockade and deposition of oil and other degraded materials in the region [56].

4.3. Androgenic alopecia

Androgenic alopecia is the phenomenon of gradual hair loss in a definite pattern due to enhance concentration and secretions of androgens. In susceptible hair follicles, testosterone is converted to dihydrotestosterone (DHT), leading to increased DHT levels that finally bind to the androgen receptor and the genes responsible for the gradual transformation of large terminal follicles miniaturized follicles gets activated by the hormone receptor [57]. This was further consolidated by the reports generated by Cela etal., where 67% of the women with alopecia areata have PCOS and elevated levels androgenic hormones [58].

4.4. Onycholysis and onychorrhexis

Onycholysis is the process of separation of the nail plate from the nail bed due to onychocorneal band [59] and onychorrhexis is the process of splitting of nails in lengthways bridges [60]. The exact reason behind this consequence is not fully understood but various researches reported that higher androgen levels in PCOS leads to exacerbated onycholysis and onychorrhexis.

5. Current treatment approach for PCOS

The cure of PCOS is unknown till now [61]. The standard care treatment for PCOS is to modify lifestyle like reduction in weight, intake of low carbohydrate in diet and daily exercise [62]. Medical treatment depends on the symptoms observed and the most common symptoms addressed in the case of PCOS are, infertility, hirsutism, menstrual disorders, and obesity. There are very few therapies that can work on a multitude of symptoms. The most difficult one is to treat infertility and hirsutism together [63] as oral contraceptives will block the ovulation or anti-androgen use, which are teratogenic for the male fetus. Therefore, these therapies are contrary to each other and thus are fruitless for treating infertility and hirsutism together. Current treatment can be divided into two categories: (i) management of infertility due to anovulation/oligo-ovulation or (ii) treatment of symptoms associated with high androgen levels (i.e., acne, hirsutism, obesity, etc. that require long term maintenance [64].

1 Treatment of infertility

2 Fluctuation in women's hormones can lead to irregularities in menstrual cycle like oligomenorrhea, amenorrhea, and anovulatory cycles that can further cause ovarian dysfunction, uterine bleeding and infertility [65]. The first line treatment includes clomiphene citrate, an antiestrogen [66]. Nowadays letrozole, a aromatase inhibitors is considered to be equally effective for the women's who want to get pregnant [67], second line treatment is use of clomiphene citrate, either alone or in combination, with metformin third line treatment is exogenous gonadotropins or laparoscopic ovarian surgery [68,69].

6. Treatment for PCOS-related symptoms

6.1. Hirsutism

(i) The first line medications for the treatment of hirsutism are spironolactone, metformin, and eflornithine [70]. Further oral contraceptives and their combinations of either progestins of norgestimate, desogestrel, or drospirenone are commonly used for hirsutism due to their low androgenic effects [71].

(ii) Mensural disorders: Mensural disorders are mostly treated with oral contraceptives. Spironolactone [72], acarbose [73], rosiglitazone [74] and metformin [75] are the medications that were effective in case of mensural irregularities.

(iii) Insulin resistance or glucose intolerance: Metformin is the first choice in this case and is reported to ameliorate insulin resistance in women with PCOS [76]. Rosiglitazone [77] and pioglitazone [78] are also reported to be effective for PCOS.

However, the use of all these medications causes unwanted side effects in women The use of clomiphene citrate may lead to visual disturbances, hot flushes, abdominal distension, mood swings, breast tenderness, dizziness, and nausea currently 6 month license is given for clomiphene citrate use. Also anti-oestrogenic effects on the endometrium and cervical mucus are not present with clomiphene citrate and letrozole [79]. Spironolactone may cause polydipsia, polyuria, nausea, headaches, fatigue, gastritis and ovulatory dysfunction resulting in polymenorrhea. [80] Nausea vomiting and gastrointestinal disturbances are the side effects associated with the use of clomiphene citrate and metformin . Further, lifelong treatment of metformin for PCOS is required and it has been reported that cessation of drug after three months of treatment may reverse all the improvements [81].

A long term treatment approach may be required in case of PCOS, thus these side effects are significant and therefore plant based drugs that offer minimal adverse effects can be considered as most suitable approach for the management of PCOS. Following is the list of plant-based constituents that have reported beneficial effects for the management of PCOS. The basic mechanism of these phytoconstituents is presented in Fig3. Their biological source, IUPAC name and chemical structure were mentioned in Table2.

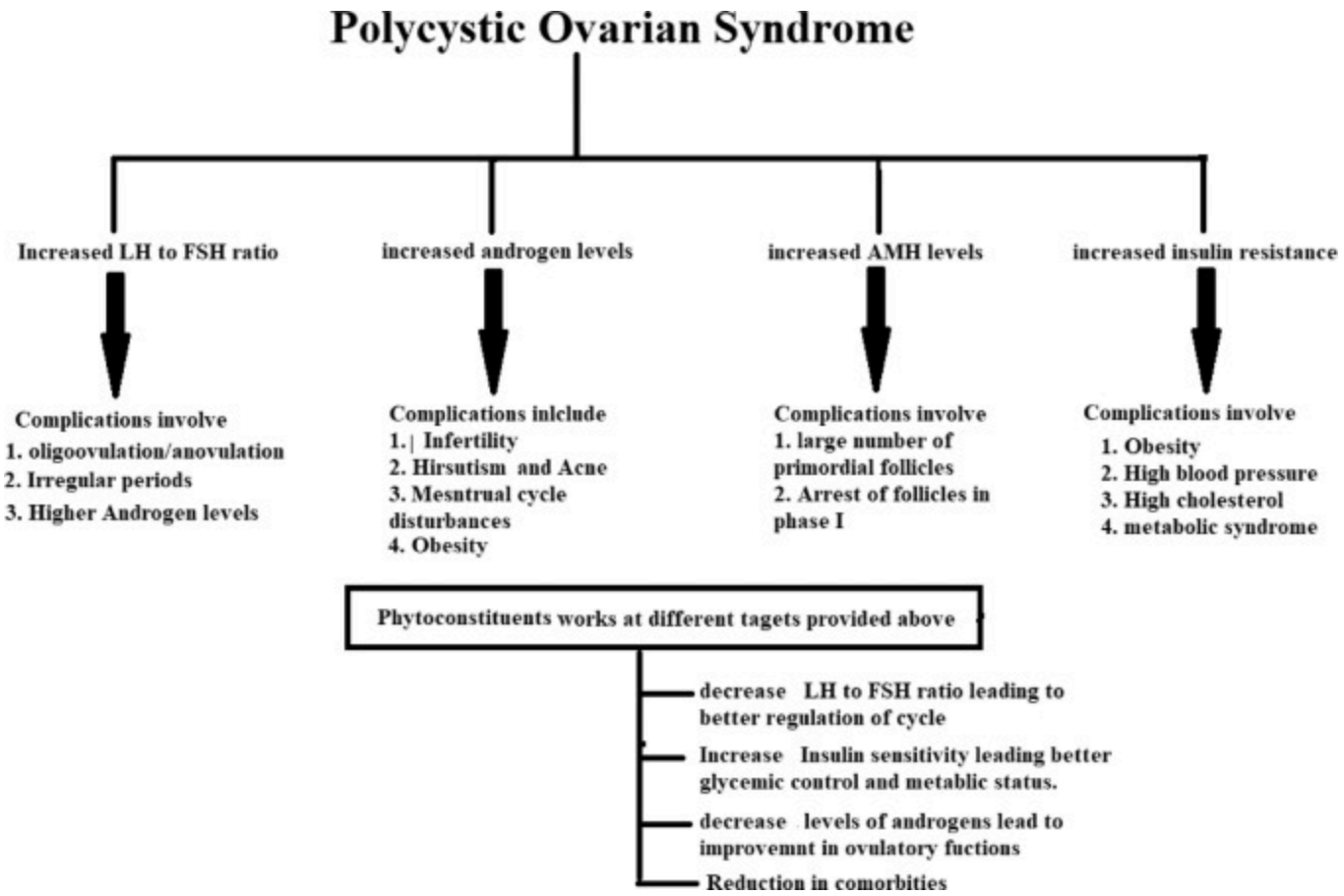

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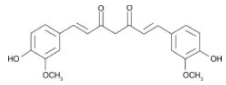
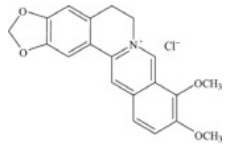
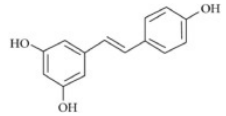
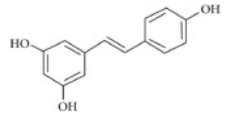
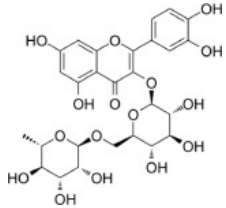
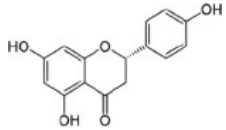
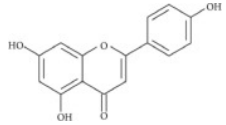
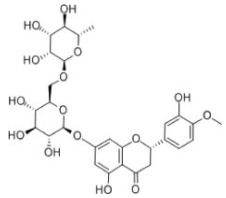
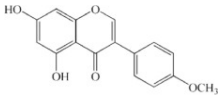
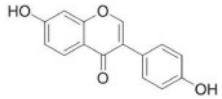
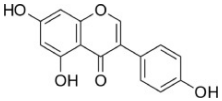
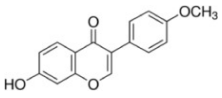
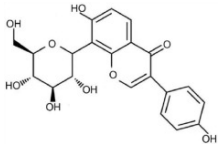
Fig. 3. PCOS complications and role of phytoconstituents (basic mechanism).

Table 2. Biological source, IUPAC name and chemical structure of phytoconstituents having potential for PCOS management.

Phytoconstituents	Biological source	IUPAC name	Chemical structure
Curcumin	Rhizomes of Curcuma longa (tumeric)	1E,6E)−1,7-bis(4-hydroxy-3-methoxyphenyl)−1,6-heptadiene-3,5-dion	
Berberine	Bark of Berberis vulgaris and Berberis aristata, Berberidaceae	16,17-dimethoxy-5,7-dioxa-13-azoniapentacyclo[11.8.0.0^{2,10}.0^{4,8}.0^{15,20}]henicosa-1(13),2,4(8),9,14,16,18,20-octaene	
Resveratrol	Vitis vinifera (red grapes)	3,5,4′-Trihydroxystilbene	
Quercetin	Camellia Sinensis, Moringa oleifera Ginkgo biloba, Hypericum perforatum, etc	3, 3′, 4′, 5, 7-pentahydroxyflvanone.	
Rutin	Buckwheat, Japanese pagoda tree, and Eucalyptus macrorhyncha	5, 7, 3′, 4′ tetrahydroxy flavonol −3- rhamnoglucoside	
Naringenin	Citrus fruits, bergamot, tomatoes and other fruits	2,3-dihydro-5,7-dihydroxy-2-(4-hydroxyphenyl)−4H-1-benzopyran-4-one	
Apigenin	Parsley, chamomile, celery, vine-spinach, artichokes, and oregano	4′,5,7,-trihydroxyflavone	
Hesperidin	Citrus fruits, including lemon, orange, lime, and grapefruit	3,5,7 trihydroxyflavanone 7-rhamnoglucoside	

Phytoconstituents	Biological source	IUPAC name	Chemical structure
Biochanin A	Trifolium pratense	5,7-dihydroxy-3-(4-methoxyphenyl)chromen-4-one	
Diazene	G. tinctoria, G. sagittalis	7,4′-Dihydroxyisoflavone	
Genistein	G. tinctoria, G. sagittalis	5,7-dihydroxy-3-(4-hydroxyphenyl)chromen-4-one	
Formononetin	Roots of Astragalus embranaceus, Trifolium pretense, Glycyrrhiza glabra and Pueraria lobata	7-hydroxy-3-(4-methoxyphenyl) chromen-4-one	
Puerarin	Root of Pueraria lobata (Willd.) Ohwi	7-hydroxy-3-(4-hydroxyphenyl)−8-[(2S,3R,4R,5S,6R)−3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]chromen-4-one	

7. Phytoconstituents for PCOS management

7.1. Curcumin

Curcumin is a natural polyphenol and is reported to offer multiple health benefit [82]. It is obtained from rhizomes of Curcuma longa and other Curcuma spp [83]. Curcumin is reported to possess various activities like antioxidant [84], anti-inflammatory [85], anti-mutagenic [86], and anticancer [87,88] and thus is used traditionally in Asian countries as medicinal herb. Various clinical and preclinical studies confirm its efficacy for PCOS as well.

Heshmati et al., 2020 proved the curcumin efficacy for PCOS. A randomized double blind clinical trial was conducted on 72 patients suffering from PCOS that were assigned randomly for curcumin (500 mg thrice daily) and placebo. The levels of

fasting plasma glucose and dehydroepiandrosterone were decreased with difference of - 4.11 mg/dL; p (adjusted)=0.048 and −26.53 microgram/dL; p (adjusted)=0.035 respectively between intervention and control groups. Further, the authors reported absence of any serious adverse effects during the entire treatment of 12 weeks [89]

Curcumin also could reduce the oxidative stress in PCOS women. Heshmati et al., 2020 supported the statement through a randomized; double blinded clinical trial conducted on seventy-two women with PCOS receiving curcumin supplementation. Curcumin (1500 mg/kg) given thrice daily increased the gene expression of oxidative enzymes Peroxisome proliferator activated receptor g coactivator 1a PGC1a from 1.123±0.277 to 1.563±0.494 (p=0.011) and activity of the glutathione peroxidase enzyme from 108.83±7.19 to 32.83±13.10 significantly. Non-significant increase in enzyme superoxide dismutase (202.77±10.23 to 241.02±13.88) and gene expression of SIRT1: sirtuin-1 (1.740±0.636 to 3.167±1.0578) was reported [89].

Jamilian et al. also evaluated the efficacy of curcumin given at dose of 500 mg/day in 60 PCOS women. A randomized double blind clinical trial for 12 weeks was performed and the result demonstrated the positive effect of curcumin like reduction in fasting glucose (p=0.002), insulin resistance (p=0.02), total cholesterol (p=0.001) and bad cholesterol (p=0.001) along with increase in insulin sensitivity (p=0.02) and good cholesterol (HDL) (p=0.01) in comparison to placebo. Additionally, beneficial effects on the gene expression of peroxisome proliferator-activated receptor gamma (PPAR-γ) (p=0.03) and low-density lipoprotein receptor (LDLR) (p<0.001) was also reported further supporting the curcumin role in managing the PCOS [90].

Sohaei et al., 2019 did a randomized double-blind clinical trial in which sixty women were chosen and randomly assigned to one of the two groups of treatment. The first group received curcumin as test drug (500 mg/d) or while the other group were given placebo two times a day up to 6 weeks. The study showed significant improvement in insulin sensitivity (p=0.020) and quantitative insulin sensitivity check index (QUICKI) (p=0.003) suggesting curcumin to be beneficial in improving the glycemia control in PCOS women [91].

Further, Reddys et al., in a preclinical study performed on letrozole induced PCOS in female Wistar rats, evaluated the potential of curcumin for PCOS given at a dose of 100 and 200 mg/kg for 15 days. The result showed marked decrease in the level of testosterone (44.10±8.63 from 140.00±5.77 ng/dl), with increase in levels of progesterone (32.93±4.06 from 12.41±0.24 ng/ml) and estradiol (30.48±1.32 from 26.73±1.41 pg/ml) in group receiving 200 mg/kg of curcumin. Also, reduction in the levels of triglycerides from 138.60±2.03 to 61.83±6.77 mg/dl, (129.30±2.01 to 68.20±9.08 mg/ml) and LDL

(83.42±2.49 to 17.40±9.59mg/ml) while increase in the level of HDL from 18.19±1.10 to 38.44±1.21mg/ml was reported. The images captured from light microscope revealed positive histomorphological changes (disappearance of cyst and appearance of hair follicles) in curcumin treated group. The authors concluded that the effect of curcumin in PCOS is similar to that observed with clomiphene citrate which is the first line therapy for infertility treatment in PCOS women [92].

7.2. Berberine

Berberine is an isoquinoline alkaloid obtained from various medicinal plants including chinensis Franch, Hydrastis [93] canadensis L [94] and Coptis japonica Makino [95]. The pharmacological properties owned by berberine are antibacterial, antiarrhythmic, anti-diabetic and anti-hyperlipidemic [96]. Various research reports have revealed and proved that berberine has great potential in improving insulin resistance and glucose uptake, metabolic index, and can result into decreased androgen levels. It also has additional effects on body composition and hyperlipidemia in women suffering from PCOS [97]. Berberine through multiple pathways and targets is reported to be beneficial for PCOS management. Kuang et al., 2020 conducted a clinical study to discover the contribution of serum inflammatory cytokines and berberine in insulin signaling pathway in the patients suffering from PCOS. The study confirmed the increased level of, IL-17a (P=0.001), IL-6 (P=0.035) and IL-1Ra (P<0.0001) in PCOS group in comparison to Non-PCOS group. Significant reduction in the expression level of mammalian target of rapamycin (mTOR mRNA) (P=0.001), and increase in the expression level of insulin receptor substrate-1 (IRS-1 mRNA) (P=0.009) was observed in the PCOS granule cells that will increase the sensitivity of insulin [98].

In another study, the effect of berberine on metabolic features of PCOS women was evaluated and compared with metformin. Wei et al., performed a trial on 89 women with PCOS. The decrease in waist circumference was (88.38±5.84vs 80.22G ±.17 in berberine group (berberine+cyproterone acetate) in comparison to metformin group (metformin+cyproterone acetate) (89.12±7.06vs 85.03±6.53) (p=0.001). A significantly greater reduction was observed for waist to hip ratio (WHR) in berberine group (0.89±0.03vs 0.82±0.04) than in metformin group (0.9G0.04vs 0.87G0.03); (P<0.001). Also a decrease in total cholesterol, and low-density lipoprotein cholesterol (P < 0.05), triglycerides along with increase in high-density lipoprotein cholesterol and sex hormone-binding globulin (P<0.05) was reported [99].

Shen et al. confirmed the protective effect of berberine on dehydroepiandrosterone induced PCOS rats. Berberine was administered for 6 weeks in a dose of 150mg/kg/day. berberine was reported to regulate the expression level of toll-like

receptor 4 (TLR4), Src family tyrosine kinase (LYN), phatidylinositol 3-kinase (PI3K), NF-kB, tumor necrosis factor-α (TNF-α), IL-1, IL-6, and caspase-3 along with decrease in cell apoptosis rate suggesting the role of berberine in PCOS management [100].

The positive effect of berberine against the symptoms of PCOS was checked in an in-vivo study conducted by Lu et al. in 2020 on PCOS mice that were divided into three groups, low-dose berberine (250mg/kg), medium-dose berberine (500mg/kg) and high dose berberine (1000mg/kg) groups. Significant decrease in body weight 17.92±1.53 and 17.68±1.27 from 19.83±1.72 was seen in the groups receiving berberine in dose of 500mg/kg and 1000mg/kg respectively. Reduction in levels of sex hormones testosterone and luteinizing hormone was also prominent in both the groups along with improvement in ovulatory function and reduction in inflammatory factors suggesting berberine to be a potential phytoconstituent for PCOS management [101].

Xiaoke et al., was granted Patent entitled “Use of berberine in the treatment of infertility and ovulatory dysfunction in year 2014 . The study was conducted over 214 patients with ovulatory and was compared with the standard drug clomiphene for 6 months treatment. The results clearly demonstrated that berberine can promote follicular discharge in patients with ovulatory infertility, and was superior to clomiphene in reducing multiple pregnancy rates, premature birth, pregnancy induced hypertension and various other complications of pregnancy in case of PCOS [102].

7.3. Resveratrol

Resveratrol also named as 3,5,4′-trihydroxy-trans-stilbene, is a plant derived polyphenol which was first isolated in 1940 from the roots of white hellebore (Veratrum grandiflorum O. Loes), then in 1960 from the roots of Polygonum cuspidatum and is now detected in around 70 species of plants including grapes. Resveratrol is reported to have beneficial effects in various diseases like cancer, diabetes, inflammation, heart diseases etc. [103]. Its efficacy for PCOS is also well documented. A clinical trial was conducted by Mansour et al. 2021, on 78 patients receiving 1000mg of the drug for period of three months to check the effect of resveratrol for PCOS. The result showed increased mensuration rate (76.47% vs. 51.61%; p=0.03) and reduced hair loss (32.10% vs. 68.00%; p=0.009) was observed while the level of lipid, insulin and androgens remains unchanged after the treatment [104].

The in vivo study performed by Rencber et al., on DHEA-induced PCOS rats also revealed the efficacy of the drug for PCOS. The rats were treated with resveratrol (20 mg/kg/day), metformin (300 mg/kg/day) and their combination. A decrease in the levels of testosterone, LH, LH/FSH, TNF-apha and tissue AMH level was noted with all the treatment groups with more marked effect in resveratrol treatment group (1.04±0.03 over 1.91±0.09 ng/ml), (0.04±0.01 over 0.11±0.01 mIU/ml), (0.30±0.05 over 0.82±0.08), (195.46±15.66 over 276.59±19.28) ng/ml and (6.17±0.26 over 9.14±0.66 ng/10 mg prot.) respectively . Further the images captured through light and electronic microscope revealed secondary, atretic and Graafian follicles. Insignificant difference was reported in between resveratrol and metformin treatment groups suggesting that resveratrol can be used as an alternative to metformin treatment [105].

7.4. Quercetin

Quercetin is a natural flavonoid that can be obtained from fruits and vegetables that mainly include citrus fruits including red grapes, onions, apples, berries, tea, nuts and seeds. Quercetin possesses various therapeutic properties like antioxidant, anti-inflammatory, anti-diabetic, anti-hypertensive and anticancer. Oxidative stress is considered to be the major factor leading to PCOS and thus several antioxidants activity have also been proved effective for the management of PCOS including quercetin [106].

The correlation between PCOS and failure of endocrine gland is also well established. The level of adiponectin gets reduced in PCOS women irrespective of obesity. Rezvan et al., evaluated the efficacy of quercetin on adiponectin-mediated insulin sensitivity in 84 PCOS women. Quercetin in a dose of 500 mg twice a day when administered for 12 weeks showed an increase in the level of total adiponectin by 6% and high molecular weight adiponectin by 4% approximately when compared to placebo. Also decrease in testosterone level (0.71 ng/dl in quercetin over 0.77 ng/dl in placebo; $p<0.001$) and L.H. (8.42 IU/l in quercetin over 8.68 IU/l in placebo; $p=0.009$) was reported along with significant reduction in HOMA-IR in quercetin group ($p<0.001$) emphasizing the role of quercetin in revamping the adiponectin-mediated insulin resistance and hormones level in PCOS women. [107].

Wang et al., studied the therapeutic effect of quercetin in reducing insulin resistance in PCOS rat model. Quercetin was reported to decrease the level of blood insulin, NF-κB, interleukin 1β, IL-6 and TNF-α. Also 58.33% recovery rate of estrous

cycle was observed after the quercetin treatment. The mechanism involved is improvement of NF-κB signaling pathway and rectification of inflammatory microenvironment of ovarian tissue in PCOS induced rat model [108].

Another in vivo study conducted by Jahan et al., showed the potential of quercetin in letrozole induced PCOS in Female Sprague Dawley rat. Quercetin in a dose of 30 mg/kg showed decrease in levels of testosterone (0.78 ng/ml±0.14 in quercetin vs. PCOS positive control 1.69 ng/ml±0.17, ($p<0.001$) and estradiol (8.85 pg/ml±0.19 in quercetin vs. PCOS positive 1.61 pg/ml±0.29) with simultaneous increase in progesterone levels (34.47 ng/ml±1.65 in quercetin vs. 11.08 ng/ml±1.17 in PCOS positive) depicting marked regulation of steroidogenesis [109].

Neisy et al., evaluated the potential of quercetin in dehydroepiandrosterone (DHEA) induced Sprague-Dawley female rats. Quercetin outstripped the insulin resistance in PCOS induced rats. Increased liver glucokinase and hexokinase was observed. Significant surge in estrogen receptor-α and glucose transporter 4 genes expression in uterus was also reported, suggesting the function of quercetin in improving the insulin resistance which is the major complication for PCOS [110].

7.5. Rutin

Rutin is a citrus flavonoid glycoside which was first obtained from the plant Ruta graveolens and is also identified in plants like passion flower, buckwheat, tea, and apple. Rutin is reported to posses several pharmacological activities that include antioxidant, anticarcinogenic, vasoprotective, neuroprotective and cardioprotective actions [111]. Transplantation of Brown adipose tissue is reported to mitigate PCOS by triggering endogenous BAT. However, clinically transplantation of BAT is not applicable. Therefore Hu et al., investigated the efficiency of rutin in BAT activation in dehydroepiandrosterone (DHEA)-induced PCOS rat. After 3 weeks of rutin treatment dramatic increase in endogenous activity of BAT was observed in positron emitted tomography-computed tomography (PET-CT), thus revamping insulin resistance and thermogenesis. Moreover, it regulated the levels of androgen hormones and ovarian steroidogenic enzymes like aromatase, 17β-HSD, 3β-HSD etc. suggesting rutin to be a novel phytochemical for PCOS treatment by activating BAT [112].

In another study by Yuan et al., with study on rats revealed that rutin can decrease fat and insulin resistance in obese mice . the mechanism involved is by increasing the activity of brown adipose tissue (BAT) and inducing the activity of the beige adipocytes in subcutaneous adipose tissue .Rutin results in SIRT1 activation and increase in expenditure of energy resulting in decrease in obesity suggesting it a potential therapeutic compound for metabolic disorders [113].

Jahan et al., checked the potential of rutin in the treatment of endocrine, oxidative and reproductive dysfunctions in PCOS induced female Sprague-Dawley rats. Rutin was administered in a dose of 100 and 150 mg/kg for 15 days. Improvement in lipidic profile (testosterone reduced to 5.77±0.68 and 8.21±1.85a from 10.19±0.76 ng/ml and progesterone level were increased to 19.66±5.34 and 24.63±3.46 from 14.26±2.70 in groups receiving rutin 100 mg/kg and 150 mg/kg respectively). Histopathological evaluation of ovary showed a reduction in number of cystic follicles in rutin treated groups providing evidence for the ameliorative effect of rutin in treating the various clinical manifestations associated with PCOS [114].

Endometriosis is also prevalent in infertile women with PCOS. Talebi et al., access the effect of rutin on edometriosis through mechanism of antioxidant and apoptosis. Administration of Rutin at dose of 3 and 6 gm reduces the expression of Bcl-2 relative density (1.0 from 2.2) and Pro-caspase9 in comparison to control ($p<0.05$). More reduction of pro caspase relative density was observed in case of group receiving 3 gm (1.5 and 2.2 in lower and higher dose group respectively from 3.5). Tunel staining result demonstrated that animals treated with rutin showed greater apoptosis . Also the concentration of anti-oxidant were increased after the 28 days of treatment with rutin [115].

7.6. Naringenin

Naringenin is a flavonoid which is obtained naturally from like grapefruit, oranges, bergamot, tomatoes etc. The properties associated with this phytoconstituent are antioxidant, anti-inflammatory, antiviral, antibacterial, antitumor, antiadipogenic and cardioprotective [116]. Hong et al., investigated the antioxidant and steroidogenic therapeutic effect of naringenin in letrozole-induced PCOS rats. Twenty eight female Sprague-Dawley rats were treated with naringenin in a dose of 20 mg/kg. The results demonstrated increased levels of reactive oxygen species, scavenging enzymes: catalase, superdimutase and glutathione peroxidase ($p<0.05$), with decrease in weight. Glucose (99 over 150 mg/dl), estradiol (3 over 5.8 pg/ml) and testosterone (275 over 360 ng/ml) levels were normalized. The normal anatomy of the ovaries was retained as depicted in histopathological studies confirming the role of naringenin in PCOS treatment [117].

In another study by Wu et al., the effect of naringenin was investigated on letrozole induced PCOS rat model. The rats were treated for two months with the flavonoid. Results clearly revealed that naringenin can significantly reduce level of testosterone (5 over 12 ng/ml), follicle-stimulating hormone (3.2 from 5.8IU/l), luteinizing hormone (6 from 10IU/L), improve insulin resistance and the ovarian tissue pathological changes, reduced body weight in the PCOS model rat in comparison to

PCOS model group ($p<0.05$). Also beneficial microbes like Butyricimonas, Lachnospira, Faecalibacterium, Parabacteroides, Butyricicoccus and Roseburia were found in feces of PCOS rat model through rDNA detection further confirming the positive impact of theflavonoid in PCOS management [118].

7.7. Apigenin

Apigenin is a flavonoid present abundantly in range of plants that include fruits (oranges), vegetables (celery, parsley, onions), herbs (thyme, chamomile basil), and plant derived beverages (beer, wine, tea,). This phytoconstituent possesses anti-cancer, antiviral, anti-inflammatory, anti-mutagenic, purgative effects, antioxidant activity and also act a radical scavenger [119]. Darabi et al., 2020 conducted study to determine its effect on hormone levels, gonadotropins, inflammatory factors, and oxidative stress in ovarian tissue of PCOS induced female Wistar rats. This research revealed a decrease in testosterone (1.4±0.1 from 2.9±0.4ng/ml), LH (4.6±0.1 from 7.6±0.4mIU/ml) and LH-FSH ratio (0.02±0.75 from 1.9±0.1) when compared to PCOS control group. The inflammatory factors like tumor necrosis factor-a, interleukin-6, and total oxidative status were reduced along with significant increase in total antioxidant capacity and superoxide dismutase in comparison to PCOS group. Further histological studies showed reduction in number of cysts, corpora lutea and thickness of theca layer .Thus apigenin can be used as an alternative treatment for PCOS management [120].

Apigenin can alter the lipid and glucose level, can prevent metabolic syndrome that may help PCOS patients to manage their symptoms. Yang et al. determined the protective role of apigenin on metabolic syndrome in high fructose fed diet-mice. The result showed improvement in insulin resistance, glucose level (reduced from approx. 11 to 9mmol/l), lipid level (HDL increased from approx. 0.6 to 1mmol/l, LDL from aprox. 1.6 to 1.1mmol/l) and HO-1 and NQO1 protein expressions that alleviate the oxidative stress concluding that apigenin can prevent many detrimental metabolic effects [121].

7.8. Hesperidin

Hesperidin, a bioflavanoid was first obtained from inside portion of orange peel. It is found abundantly in several citrus fruits that include lime, orange, grapefruit and lemon. This phytochemical posses several activity like anti-inflammatory, anti-microbial, type-II diabetes, cardiovascular and skin lightening . Lifestyle modification like sustainable weight loss, exercise and dietary modification has also played role in management of PCOS and Hesperidin can enhance the effectiveness of lifestyle modification. Yari et al., conducted randomized controlled trial in 49 subjects receiving Hesperidin (500mg twice a

day) and brown flaxseed (30g milled) in combination along with lifestyle intervention. Result showed non-significant reduction in waist circumference from −6.75cm to −3.57cm. Significant improvement in lipidic profile, atherogenic indices, glucose homeostasis parameters, and inflammatory biomarkers were also reported in comparison to control group ($p<0.05$). Reduction in blood pressure was also observed (−5.66 over −1.56mmHg) $P=0.049$. Thus this compound can also have potential for PCOS management [122].

Hespridin has been reported to improve insulin resistance. The same has been proved by Peng et al., using rat model of alloxan and high fat diet induces insulin resistance. The hesperidin was administered at dose of 100mg/kg and result showed hesperidin ability to regulate glycolysis and gluconeogenesis. Reduction in Blood glucose (from 19.8 to 10.6mmol/L), Insulin resistance index (approx.. from 2.5 to 1.3) was observed when compared to model group. This effect is produced by inducing insulin receptor (IR) and phosphoinositide-dependent kinase 1 (PDK1) phosphorylation. Also decrease in the activity of glucose-6-phosphatase and phosphoenolpyruvate carboxykinase was reported [123]

In vitro study conducted by Shoorej et al., has given initial evidence by investigating the hesperidin effect at different concentration on growth and maturation of preantral follicle isolated from ovaries of immature mice. Hesperidin at concentration of 10, 22.5, and 50μmol/L was studied in different groups. The 12 days culture period showed significant increase in the percentage of rate of survival, formation of antrum, obtained metaphase II oocytes, 17β-estradiol (2785 over 1872pg/mL) and progesterone (36 over 17ng/ml) secretion in the group supplemented with hesperidin 50μmol/L when compared to control ($p<0.05$). The mean diameter of follicles was increased in all groups with maximum for group Hesp 50 (approx.50μm). Moreover, addition of hesperidin at conc of 50μmol/L showed increased fertilization rate and embryo development for the first time in this study suggesting hesperidin to be future phytochemical for infertility treatment. However, in vivo studies and clinical trials are required to explore its effect on PCOS [124].

7.9. Phytoestrogen

Phytoestrogen are natural plant derived isoflavanone, mainly found in soy based products that offers several health benefits for diseases related to cardiovascular, osteoporosis, cancer and menopausal symptoms [125]

Phytoestrogens such as Biochanin A, Daidzein, Genistein, formononetin and Puerarin are reported to have beneficial effects on PCOS management. The secretion and metabolism of androgen and estrogen gets disrupted in PCOS women, that leads to

increase serum concentrations of androstenedione, testosterone and dehydroepiandrosterone. Phytoestrogen are very similar to estrogen 17-β estradiol and diethylstilbesterol in terms of size and molecular structure and thus can bind to estrogenic receptors and exhibit anti-estrogenic effects, thus balancing the level of hormones in PCOS women [126].

To demonstrate the effectiveness of soy-isoflavone or phytoestrogen for PCOS Jamilian et al., 2016 conducted randomized, double blind, placebo controlled trial .Women diagnosed with PCOS that includes were administered phytoestrogen mixture consisting 37.5 mg genistein, 10 mg daidzein, and 2.5 mg glycitein for 12 weeks. Result demonstrated significant reduction in free androgen index (−0.03±0.04 from +0.02±0.03; $P<0.001$) and serum triglycerides (−13.3±62.2 from +10.3±24.5 mg/dL; $P=0.04$, insulin level in serum (−1.2±4.0 from 2.8±4.7)μIU/ml; $P<0.001$. Significant increase in plasma glutathione level and decrease in monoaldehyde levels also suggested positive effect of phytoestrogen for PCOS management [127].

In another in-vivo study conducted by Rajan et al., 2016 examined phytoestrogen role in letrozole induce PCOS model of Sprague–Dawley rat . Mixture of phytoestrogen (genistin, daidzin and its aglycone form genistein and daidzein accounting for 59.91, 12.05, 23.53, and 4.49% respectively) 50 and 100 mg/kg was administered orally for 3 weeks consecutively. The changes caused by letrozole induced PCOS was reversed with maximum effect in high dose receiving group. Decrease in body weigh gain, diestrous days (approx. 40 from 79%),testosterone level (55 from 115 ng/ml), 17β-HSD enzyme activity and oxidative stress was observed. Moreover histological images showed that treatment with phytoestrogen resulted in normal granulosa cell layer and well developed antral follicles [128].

7.9.1. Biochanin A (BCA)

Biochanin A is a isoflavanone phytoestrogen present in soy based products mainly in red clover named scientifically Trifolium pratense [129]. Phytoestrogen have can bind to estrogen receptors and thus may affect reproductive function in females. Biochanin A is reported to posses anticancer, neuroprotective, anti-inflammatory, antioxidant, anti-microbial and hepatoprotective activity [130]. It also possess biological activity similar to estrogen . Biochanin is also reported to have beneficial effect in reproductive process and thus can manage PCOS.

Nynca et al., 2013 evaluated in-vitro effect of biochanin A using invitro model of porcine granulosa cells. The cells were preincubated and cultured in Biochanin A(0.0.05, 0.5,5, 50 mM) for 48 h. Biochanin A was reported to inhibit the basal progesterone level significantly from follicles by leutilized granulosa cells while the effect on estradiol secretion remains

unaffected. The treatment does not cause any effect on cell viability. Also enhanced expression of estrogen receptor β immunoexpression was observed in the cells from both medium and large size follicles ($p<0.05$). further studies are required to explore is effect in PCOS [131].

7.9.2. Daidzein

Daidzein is found in plants like legumes, soyabeans, mug beans and green beans in significant amount. Many studies have reported numerous health benefits of Daidzein for several diseases like cancer, cardiovascular and inflammation . Reports confirming daidzein and its metabolite equol positive role in female reproductive and ovarin cell function has been reported.

Medigovic et al., conducted in-vivo study to investigate the effect of Daidzein in 12 months old female rats for hormonal and functional parameters of the pituitary ovarian axis. 35 mg/kg of Daidzen or Genistein or0.625 mg/kg of estradiol was administered subcutaneously for 28 days. After the treatment of Diadzen and Genistein less anteric follicles and more healthy primordial and primary follicles were reported. Estradiol results in increase in atretic follicles and mostly causes negative impact on ovaries. Diadzein also results in increase progesterone level by 34% and decrease in testosterone levels by 49% ($p<0.05$). Further both the drugs Diadzein and Genistein decreases CuZnSOD (Copper Zinc superoxide dismutase) and CAT (catalase) activity in female rat ovaries with more pronounced effect was observed with Diadzein [132].

Diadzein have proven activity with other phytoestrogen in PCOS patients however its individual therapeutic effect is yet to be explored in PCOS patient.

7.9.3. Genistein

Genistein is another isoflavone phytoestrogen that binds to estrogen receptor ERα and Erβ. In 1899 the compound was first isolated from Genista tinctoria L and now is found to present as main secondary metabolite in Trifolium species and in Glycine max L. (synonym Soja hispida) [133] .

Haddad et al., 2020 explored Genistein for its influence on Sprague Dawley rats with premature ovarian failure (POF) induced by 3.2 Gy γ-radiation. The rats were treated with either Genistein (5 mg/kg i.p) or Ethinyl estradiol (0.1 mg/kg s.c) given once in a day for 10 days. Genistein administration leads to decreased atretic follicles . The diminished serum levels of estradiol

(approx. 100 from 50pg/ml) and anti-Müllerian hormone (12 from 7ng/ml) due to radiation was restored after the treatment with Genistein. Also the expression of Bacl2 was augmented and Bax was suppressed along with improvement in granulosa cell proliferation. Oxidative stress markers level like GSH (67.77±7.98 over 24.09±8.09μg/mg) and glutathione peroxidase activity (4.89±0.53 over 2.87±0.08U/g tissue) was also improved suggesting Genistein to be a novel treatment modality for premature ovarian function in females [134].

Zhang et al., 2019 studied genistein estrogenic property on expression of follicle-stimulating hormone receptor (FSHR) and luteinizing hormone receptor (LHR) in rat ovaries with PCOS. Genistein was administered at dose of 5,10 and 20mg/kg daily in low dose (L-gen), middle dose(m-gen) and high dose group (H-gen) respectively. After treatment significant reduction was observed in testosterone (7.269±0.625 over 8.341±0.425nmol/L), LH (3.225±0.405 over 4.518±0.477ng/ml) and LH/FSH ratio 1.385±0.184 over 2.607±0.446). Also the concentration of progesterone was markedly increased (5.177±0.453vs 1.645±0.468μg/L) in group receiving H-Gen in comparison to PCOS model control group. Further LHR protein expression was enhanced and FSHR protein expression was suppressed resulting in improvement in ovarian function [135] .

In another study Chi et al., 2018 identified the genistein role on expression of Bcl-2 mRNA and Bax mRNA in rat ovaries with PCOS by in-situ hybridization and concentration of Bcl-2 and Bax protein was determined by ELISA. Genistein in dose group was administered either at the concentration of 5 (L-gen), 10(M-Gen) or 20(H-Gen) mg/kg of body weight. The result demonstrated increased expression of Bcl-2 mRNA and Bcl-2 protein in comparison to model group ($p<0.01$) while Bax expression was suppressed. Further the diameter of cystic follicles was reduced significantly when compared to model group ($p<0.05$) with maximum reduction of 0.583±0.066 from 0.611±0.076cm^2 was observed in high dose group recommending genistein to be a potential phytoestrogen for management of PCOS [136].

The reported antioxidant activity of GEN on ovarian tissue of rats induced by PCOS was explored by Rajaei et al., 2018. Treatment with GEN 1mg/kg body weight for 14 days lead to significant reduction in the malondialdehyde levels (approx. 24 from 38μmol/mg) with increase in the total antioxidant capacity(approx. 2.0 from 0.06mmol/L), glutathione peroxidase (approx. 149 from 71U/mg), and superoxide dismutase activities (approx. 15 from 6U/mg) in comparison to PCOS model group. Further images from histological investigation revealed GEN was able to restore normal morphology of ovary with reduction in atretic follicles suggesting GEN administration may provide beneficial effects in PCOS patients [137].

7.9.4. Formononetin

Formononetin is another phytoestrogen isoflavone present in roots of Astragalus embranaceus, Trifolium pretense, Glycyrrhiza glabra and Pueraria lobata. Formononetin have anti-inflammatory, cardiovascular, anti-diabetic, antioxidant, anticancer, neuroprotective00. and anti-microbial properties. It has been reported to regulate lipid, glucose and insulin [138]. Oza et al., orally administered 10, 20 and 40 mg/kg of the drug in Streptozocin induced Sprague Dawley rats diabetic model. Group receiving higher dose of drug showed maximum improvement in plasma glucose level (approx. 13 from 28 mmol/l), TG (approx. 0.6 from 3.0 mmol/l), LDL (approx. 1.1 from 2 mmol/l) and HDL (approx. 0.4 from 1.4 mmol/l) significantly ($p<0.01$). Formononetin also plays important role in reducing oxidative stress. However there is no report available for formononetin that can explore its efficacy for PCOS. Due to its structure similarities with estrogen and positive effects in reducing lipid level, glucose level, improving insulin index and reducing oxidative stress suggest that it can be a potential compound for PCOS management [139].

Puerarin is a isoflavanoid found in the root of Pueraria lobata (Willd.) Ohwi which is commonly known as Gegen in China. It is traditionally used as herbal medicine for the treatment of diabetes [140]. Due to its reported effectiveness for several metabolic disorders,

Li et al., 2021 conducted randomized clinical trial on Chinese women to evaluate its potential for PCOS. Women's having premature ovarian failure were divided in two groups i.e. obese(Body mass index, BMI >25 kg/m^2) and non-obese groups . Standard treatment (orally Diane-35,one tablet daily plus metformin, 1.5 g/d) were given to the patients along with Puerarin (150 mg/d) for a period of three months. The group receiving additional treatment of Puerarin showed significant improvements in superoxide dismutase (SOD),and sex hormone binding globulin (SHBG) in both obese and non-obese patients when compared to the group not receiving additional treatment of Puerarin. Also obese women's showed significant decrease in systolic blood pressure, total cholestrola and testosterone levels suggesting that puerarin can be used effectively for PCOS management [141].

In another study by Cun et al., 2015 the effectiveness of puerarin injection on resistance to insulin and sex hormones was evaluated in dehydroepiandrosterone induced 92 female rats. The rats were divided into two groups, control group receiving metformin orally and observational group receiving transabdominal injection of puerarin. The effectiveness rate was significantly higher in observational group (approx. 85%) in comparison to control group (approx. 65%) ($p<0.05$). The level of

fasting glucose, fasting insulin and reproductive hormones were reduced in observational group in comparison to control group($p<0.01$) concluding that Puerain can be used to manage the symptoms associated with PCOS [142].

8. Regulatory aspects of phytoconstituents

Plant-based therapeutic agents are an essential alternative to modern medicine. These plant-derived therapeutic agents were thought to be less toxic as compared to synthetic ones. However, due to the absence of regulatory control, a growing number of reports highlight their side effects for various diseases. The main reason behind this is the unavailability of sufficient data about their quality, safety, and efficacy. Therefore, it is vital to perceive the dangers related to the use of natural pills so that their safety can be assured for public health [143]. There are quite a few demanding situations that should be faced while enforcing guidelines or regulations in the discipline of phytoformulations. Challenges regularly encountered in most countries are common and related to the regulatory status, quality control, monitoring safety, and insufficient expertise of dynamics and kinetics inside countrywide regulatory authorities. [144]. These products are not registered in several countries, sold freely by medical agencies, and thus available to customers without prescription [145]. The World Health Organization's (WHO) Traditional Medicine (T.M.) Strategy 2014–2023 is to increase knowledge sharing and to provide guidance on regulatory and quality control to promote safety, quality and efficacy of phytopharmaceuticals [146]. In India, the 2015 regulatory requirement for phytoformulation is under the control of the Central Drugs Standards Control Organization (CDSCO) that mandates the regulatory submission necessities for scientific data on safety, efficacy, and quality of phytoformulations evaluated and marketed on comparable strains to synthetic, chemical moieties. A new appendix I B has been added in schedule Y that detailed the data required to be submitted to conduct a clinical trial or import or export or manufacture any phyto-based formulation in India [147]. These new regulations are comparable to those of the USA, China and will promote research and development in phytopharmaceuticals [148]. Currently, several regulatory frameworks are available, but the missing part is the harmony between the regulating agencies [149, 150]. Therefore, a global harmony between the regulatory agencies is required so that only the safe and effective composition can enter the market and public health safety can be assured [151]. Also, knowledge sharing between the agencies, physicians, and patients about the use and safety must be done to develop trust. These potential phytoconstituents can be used effectively.

9. Conclusion

In the current scenario, the prevalence of PCOS is getting increased and tits management is essential to improve the quality of life. Currently, available medications regulate the mensural cycle, androgen level, obesity, ovulation and insulin resistance. The treatment approach is different for each symptom, and effective treatment to manage PCOS is still a challenge. In recent years phytoconstituents have gained much attention due to the less severe side effects associated with them. Further well-designed preclinical and clinical trials have proved that these phytoconstituents can reduce FSH, L.H., testosterone and insulin resistance. Curcumin, berberine, and resveratrol can serve as a potential alternative for clomiphene citrate and metformin for PCOS management. Due to the absence of proper regulatory control, minimal information is available regarding their safety, quality, and efficacy. This limitation, however, must not frame a shadow over these phytoconstituents. However, it must instead emphasize conducting more continued research so that these agents can be used more effectively for PCOS and benefit humanity. In the future, phytoconstituents may serve as a practical and patient compliant treatment approach for PCOS management.

Declaration of Competing Interest

The authors reflect no conflict of interest.

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Anticancer potential of indole derivatives: an update

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Abstract

The heterocyclic indole is one of the most prevalent pharmacophores in nature. It has been a highly privileged scaffold for designing targeted and anticancer therapeutics. Countless fused heterocyclic templates have been developed with diverse physicochemical and biological properties. Due to their versatile ethanobotanical and pharmacological values, indole and its derivatives seek high demand in the chemical and healthcare sectors. Extensive anticancer research has been conducted in this decade to evaluate their efficacy for diverse malignancies. The chapter explores the anticancer activity of natural and synthetic indole derivatives expressed through targeting different biological receptors and enzymes.

Keywords: anticancer agents; heterocyclic; indole derivatives; receptors

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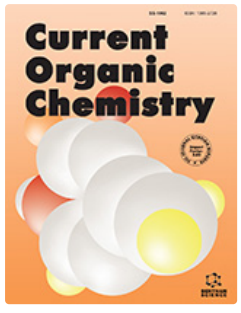

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Review Article

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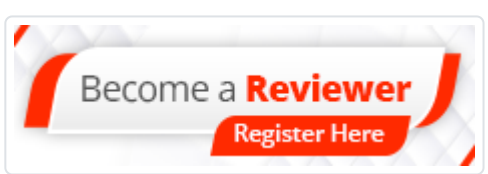

Abstract

In nature, flavonoids constitute a relatively diverse family of aromatic molecules such as flavones, flavonols, flavanones, isoflavone, chalcones, and their derivatives. Natural and synthetic flavonoids have reported diverse biological activity including antimycobacterial, antimicrobial, antiproliferative, antiarrhythmic, antiviral, antihypertensive, antioxidant, and anti-inflammatory. Flavonoids have garnered much attention as potential targets for nutraceuticals and pharmaceuticals. The recent development of “Green Chemistry” has enabled us to manipulate biosynthetic pathways to generate a library of synthetic flavonoids and to diminish the hazards for human health and environmental pollution from conventional methods. This paper presents an exhaustive review of the green synthesis of flavonoids. Green chemistry is the need for the day; hence chalcones can be synthesized in an eco-friendly manner without using solvents. The chalcone synthesis involves the solvent-free solid-state trituration between

acetophenone derivatives and substituted benzaldehydes in the presence of NaOH/KOH as a base (Claisen-Schmidt reaction). Using these chalcone derivatives, synthesis of flavonoids can be done. In the pharmaceutical arena, economical bulk production of different types of flavonoids has been successfully established by green chemistry techniques.

Keywords: Green synthesis, flavonoids, chalcones, microwave irradiation, grinding, Claisen-Schmidt condensation.

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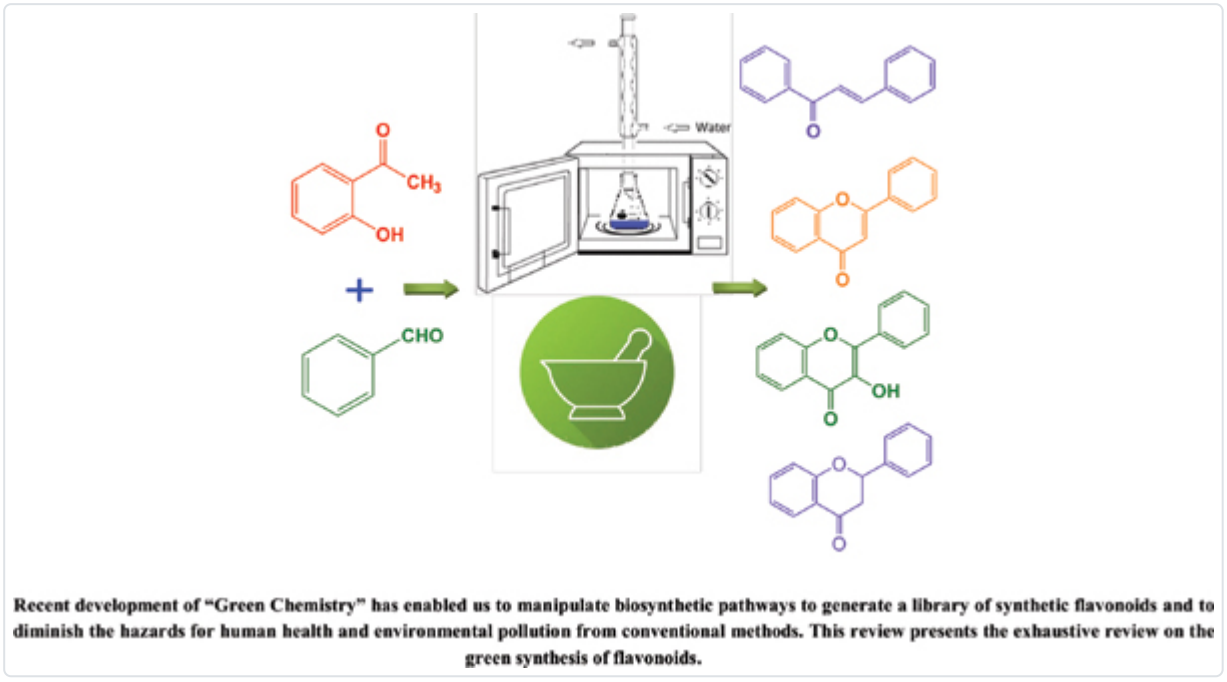

Recent development of "Green Chemistry" has enabled us to manipulate biosynthetic pathways to generate a library of synthetic flavonoids and to diminish the hazards for human health and environmental pollution from conventional methods. This review presents the exhaustive review on the green synthesis of flavonoids.

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Abstract

Orodispersible film (ODF) formulations are promising and progressive drug delivery systems that are widely accepted by subjects across all the age groups. They are traditionally fabricated using the most popular yet conventional method called solvent casting method. The most modern and evolving method is based on printing technologies and such printed products are generally termed as printed orodispersible films (POFs). This modern technology is well suited to fabricate ODFs across different settings (laboratory or industrial) in general and in a pharmacy setting in particular. The present review provides an overview of various printing methods employed in fabricating POFs. Particularly, it provides insight about preparing POFs using inkjet, flexographic, and three-dimensional printing (3DP) or additive manufacturing techniques like filament deposition modeling, hot-melt ram extrusion 3DP, and semisolid extrusion 3DP methods. Additionally, the review is focused on patenting trends in POFs using ESPACENET, a European Patent Office search database. Finally, the review captures future market potential of 3DP in general and ODFs market potential in particular.

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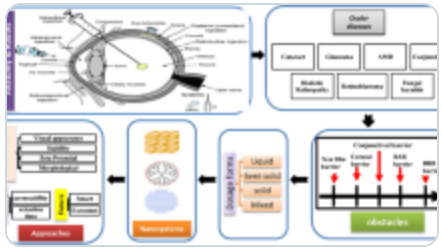

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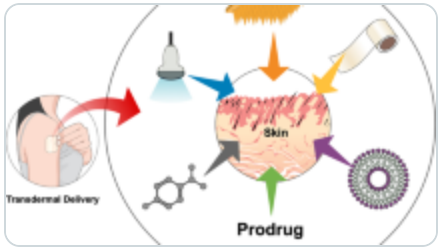

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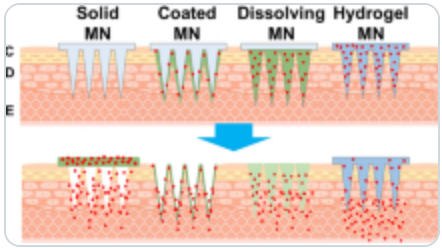

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Biomedical Applications of Quaternized Chitosan

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Abstract

The natural polymer chitosan is the second most abundant biopolymer on earth after chitin and has been extensively explored for preparation of versatile drug delivery systems. The presence of two distinct reactive functional groups (an amino group at C2, and a primary and secondary hydroxyl group at C3 and C6) of chitosan are involved in the transformation of expedient derivatives such as acylated, alkylated, carboxylated, quaternized and esterified chitosan. Amongst these, quaternized chitosan is preferred in pharmaceutical industries owing to its prominent features including superior water solubility, augmented antimicrobial actions, modified wound healing, pH-sensitive targeting, biocompatibility, and biodegradability. It has been explored in a large realm of pharmaceuticals, cosmeceuticals, and the biomedical arena. Immense classy drug delivery systems containing quaternized chitosan have been intended for tissue engineering, wound healing, gene, and vaccine delivery. This review article outlines synthetic techniques, basic characteristics, inherent properties, biomedical applications, and ubiquitous challenges associated to quaternized chitosan.

Keywords: quaternized chitosan, antimicrobial, biocompatibility, biomedical, vaccine, wound healing

1. Introduction

Chitosan, an aminoglucopyran polysaccharide, is widely utilized in pharmaceuticals, cosmeceuticals, biomedicals, agricultures, foods and packaging sectors owing to its inherent properties including biodegradability, biocompatibility, and non-toxicity [1,2]. The natural biopolymer chitosan is predominantly obtained from the exoskeletons of marine crustaceans, mollusks, insects, and fungi through an alkali deacetylation process. Figure 1 illustrated the schematic developmental process of quaternized chitosan from native chitin [3]. In contrast to natural occurring chitin, chitosan is very soluble in acidic solvents and fluroalcohols. Chitosan is a weak base, possessing pKa ranging from 6.2 to 7.0, and tends to be biodegradable in both in vitro and in vivo into non-toxic metabolites. It can be easily digested by lysozyme into non-active oligosaccharide and is thus a desirable component for designing absorbable sutures, osteoconductive implants and tissue scaffolds [4]. The biological functions of chitosan biopolymer are based on its molecular weight, degree of acetylation, charge density and extent of quaternization [5]. The physicochemical and biological properties of chitosan are primarily affected by the degree of deacetylation that directly impact on its molecular weight, pKa, crystallinity, hydrophilicity, degradation, and biological actions [6,7]. A degree of deacetylation value close to 0% or 100% prolongs biodegradation and cell adhesion, whereas transitional values of the degree of deacetylation display speedy degradation rates of chitosan. The physicochemical properties including the degree of acetylation and the molecular weight of chitosan and its derivatives are accountable for its biological responses [8]. USFDA-approved chitosan is highly utilized in tissue engineering, skin regeneration and wound healing drug delivery systems [9]. The presence of inter- and intramolecular hydrogen bonds demonstrates crystalline behaviour, which accounts for its poor aqueous solubility. The limited solubility in a wide range of physiological solutions restricts the use of chitosan in designing drug delivery systems [10].

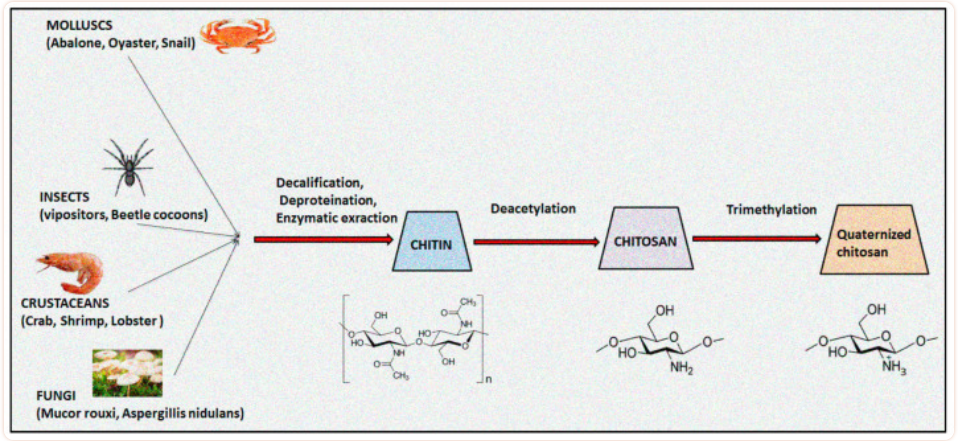

Figure 1

Schematic developmental process of quaternized chitosan from native chitin.

Conformational changes in the chitosan skeleton are reliant on local environmental conditions including the pH, pKa, N-substitution group, process temperature and types of acids. The functional groups (hydroxyl and amino) contribute an essential role for imparting solubility to the chitosan molecule. At low pH, the attached amino group undergoes protonation, solubilizes and provides positive charge to the medium, offering strong electrostatic interaction with negative charge cell components. Moreover, the pKa of amino group highly depends on the degree of acetylation (DA); hence, the solubility of chitosan is also reliant on DA [11].

Various chemical modification such as acetylation (insertion of anhydride and acyl chloride) [12], alkylation (alkyl group) [13], carboxylation (glyoxylic acid, chloroalkanoic acid) [14], quaternization (quaternary ammonium salts) [15], esterification (sulphuric acid, phosphoric acid and chlorosulfonic acid) [16] and etherification (chloroacetic acid, ethylene oxide, dimethyl sulphate) [17] at the C2, C3 and C6 position of chitosan are carried out to improve its physicochemical (enhanced aqueous solubility, improved absorption, high bioavailability, etc.) and biological properties (improved antimicrobial action and antioxidant, high penetration across cell membrane, mucoadhesiveness, etc.) Figure 2 displays the structural differentiation between chitosan and quaternized chitosan [18].

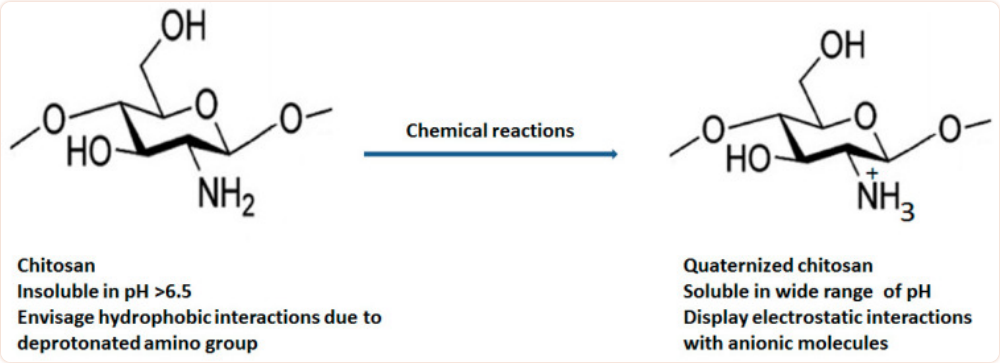

Figure 2

Structural differentiation between chitosan and quaternized chitosan.

2. Quaternized Chitosan Derivatives and Physicochemical Properties

The quaternization of chitosan involves the insertion of a hydrophilic group via any of three methods: direct quaternary ammonium substitution, epoxy derivative open loop and N-alkylation. A high degree of substitution provides better aqueous solubility and enhanced antimicrobial action, and lessens cytotoxicity with innate mucoadhesiveness and efficient penetration. The degree of quaternization and molecular weight are a few essential parameters that elicit physicochemical and biological actions (Table 1). Figure 3 compiles drug delivery approaches and biomedical applications of quaternized chitosan [19].

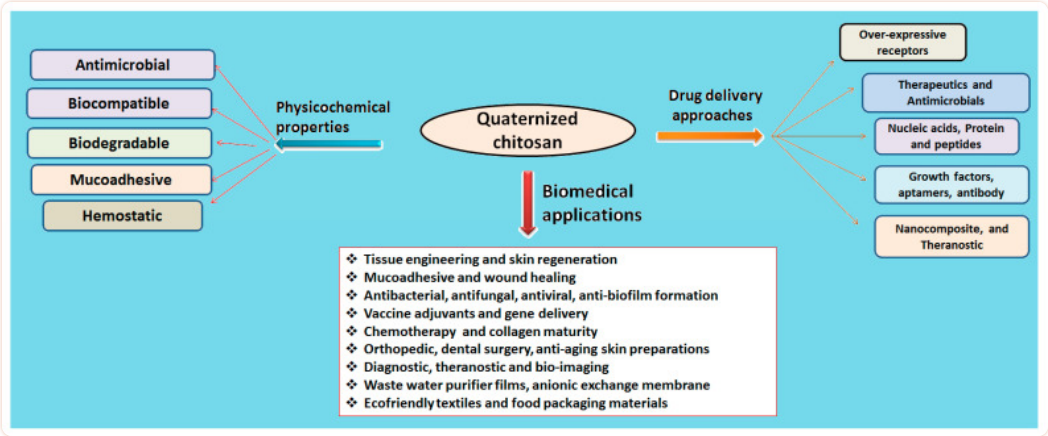

Figure 3

Quaternized chitosan and its physicochemical and drug delivery approaches.

Table 1

Effect of parameters influencing the biological responses [20,21].

Parameters	Responses
Degree of quaternization (<65%)	Increased cytotoxicity Increased mucoadhesiveness Decreased anticoagulation effect
Degree of quaternization (≥20%)	Increased antimicrobial action in pH = 7.2 No effect on antimicrobial action in acidic pH
Degree of substitution (<1%)	Increased antioxidant property
Degree of substitution (<25%)	Increased antithrombin action and acid-binding capacity
Degree of substitution (>1%)	Decreased moisture absorption and retention ability
High concentration	Increased particle size, aggregation, zeta potential, cytotoxicity Decreased knockdown efficiency and poor transfection efficacy

Quaternization not only enhances solubility but also escalates chargeability and antibacterial efficacy [22].

The mechanical property plays a vital role in imparting biomedical application. It is observed that mechanical property of chitosan enhances on increasing its concentration owing to high crystallinity. Jana et al. (2012) investigated the comparative tensile strength of scaffolds fabricated from chitosan solution (4–12%). As the concentration of chitosan increased in scaffold, augmented mechanical strength (from 1.74 MPa to 17.99 Mpa) was displayed through XRD patterns. The degree of protonation and extent of crystallinity mediated the high strength of chitosan [23,24,25]. Britto et al. (2007) synthesized quaternary salts of chitosan through dimethylsulphate reaction. The mechanical strength, Young's modulus and maximum strain were compared to the unmodified, N-alkylated and quaternized chitosan films, which are well depicted in Figure 4. Unmodified chitosan film exhibited higher mechanical strength compared to quaternized (N-dodecyl chitosan) and alkylated (butyl chitosan) in order of 44.0 Mpa > 38.3 Mpa > 13.4 Mpa, respectively [26,27,28].

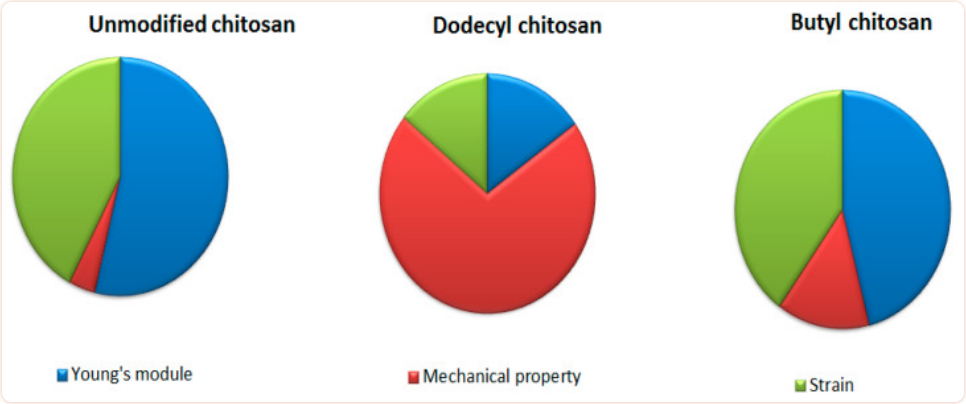

Figure 4

Comparative mechanical properties of chitosan and its derivatives.

2.1. N,N,N-Trimethyl Chitosan Chloride

The quaternization (trimethylation and triethylation) of decorated amino groups in molecular structure of chitosan is carried out by treating it with methyl iodide at a high temperature in alkali medium. Subsequently, the degree of quaternization of different grades of deacetylated chitosans is optimized through the modification of a number of reaction steps and time. N,N,N-trimethyl chitosan chloride (TMC), the most abundantly explored QCh derivative, has been utilized in the formulation of pharmaceutical products. It is obtained through the methylation of the amino group at the C2 site of chitosan backbone (Figure 4). QCH substituted through N-(3-chloro-2-hydroxy-propyl) trimethylammonium chloride has increased pharmacokinetic and antimicrobial properties. The extent of N-substitution (ES) affected antimicrobial action of QCH. The literature envisaged that when ES is 20% high, the efficacy of QCH derivative against pathogenic *E. coli* (16 to 64 µg/mL) and *S. aureus* (8 to 64 µg/mL) is enhanced. Furthermore, N-methylated, N-arylated, N,N-dimethylaminophenyl and pyridyl-substituted QCH are very soluble in water irrespective of the pH and exhibited superior antibacterial efficacy [29].

The multifunctional quaternized chitosan derivatives, their synthesis and biomedical applications are displayed in Figure 5 [30]. Other byproducts such as 6-O-methylated, 3-O-methylated and N, N-dimethylated chitosan are infrequently used due to their unfavourable properties. The very first TMC was synthesized by Terayama and coworkers and was called macramin [31,32]. A higher degree of quaternization achieved after O-methylation of chitosan at position 3-OH and 6-OH results in less soluble trimethyl chitosan

iodide. The methylation process is considerably decreased through recycling of the basic reaction until the desired product is achieved. Furthermore, preparation of trimethyl chitosan (N,N,N-trimethyl chitosan) is accomplished through an ion exchange process that possesses high solubility and basicity. Reports have cited that the intermediate degree of quaternization (~40%) evidences the highest solubility regardless of the molecular weight and degree of acetylation of chitosan due to the replacement of the attached primary amino functional group with quaternary amino groups at the C2 position [33]. The molecular weight of TMC increases during the course of reductive methylation because the methyl group is added to the previously attached ammonium group of the repeated monomers. Moreover, a significant decrease in molecular weight is noticed after treating with strong alkali at an elevated temperature, which causes degradation of the polymeric chain. Furthermore, an increase in the degree of quaternization of TMC polymers causes a decrease in the intrinsic viscosity [34]. The mucoadhesive property decreases with an increase in the degree of quaternization, owing to the alteration of conformation of polymers during the quaternization process, which affects the interaction between fixed positive charges on each polymeric chain at C2 position. It also decreases the polymer–polymer flexibility. Furthermore, attached functional groups (methyl, ethyl, propyl, benzyl, etc.) on amino groups may hide positive charges and this causes a steric effect. Both decrease the polymeric chain flexibility and produce steric effects that influence the extent of charge transfer between cationic TMC and anionic sialic acid present in the mucus, thus resulting in inferior mucoadhesiveness [35].

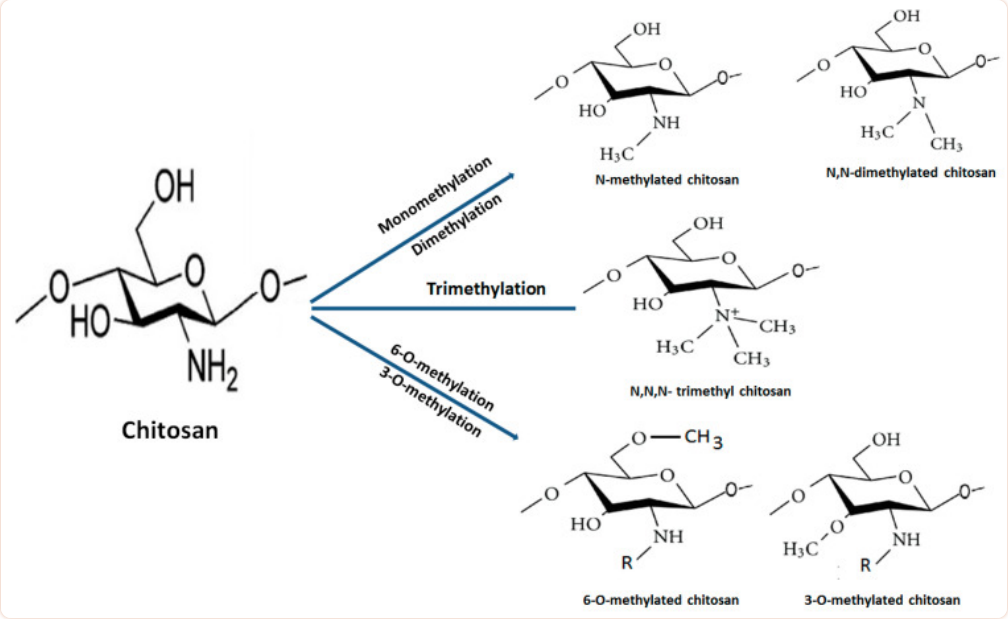

Figure 5

Different pathways for synthesis of methylated chitosan from native chitosan.

2.2. N-[(2-Hydroxyl-3-Trimethyl Ammonium) Propyl] Chitosan

N-[(2-hydroxyl-3-trimethyl ammonium) propyl] chitosan or HTCC is the second most-popular QCh prepared via alkylation process involving insertion of quaternary ammonium group at the outside the chitosan structure. Lang et al. 1980 synthesized the first HTCC through chitosan modification [36]. The reagent 'glycidyl trimethylammonium chloride' (GTMAC) is often used for direct replacement of hydrogen from attached amino and hydroxyl functional groups from chitosan at the C6 position to obtain O, N-substituted quaternized chitosan (HTCC), which enhances the aqueous solubility and superior antibacterial efficacy (Figure 6) [37]. The generated HTCC polymers have different degrees of quaternization that refer to the extent of positive charge [38].

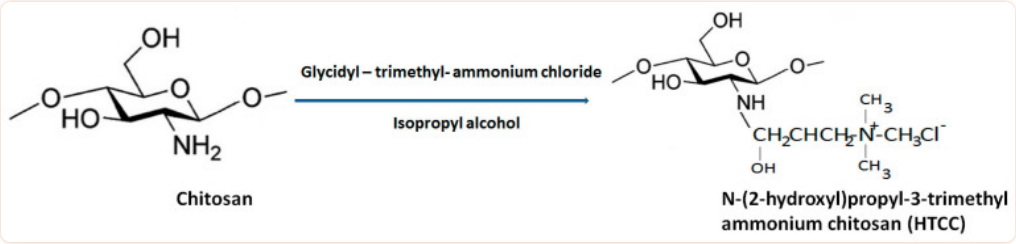

Figure 6

General synthesis of HTCC from biopolymer chitosan.

HTCC presents non-toxicity, improved aqueous solubility, and modified antimicrobial action along with biocompatibility and bioavailability features. Xiao et al. (2012) demonstrated that HTCC is more amorphous than crystalline chitosan. Quaternization weakens inter-/intra molecular hydrogen bonds and results in unorganized HTCC polymer that not only facilitates solubilization but also favours better absorption due to the diffusion of free water molecules from the HTCC chains [39].

Similarly, increased antimicrobial action is also defined due to abundant positive charge on HTCC that is attracted by negative surface charge present on the bacterial cell surface. HTCC encompasses permanent positive charges on its surface. The physicochemical properties of HTCC are highly reliant on the degree of quaternization. Wang et al. (2018) studied the effect of quaternization on the physicochemical and biological properties of HTCC. The outcomes revealed that the apparent viscosity, solubility, and elasticity are amplified by an increase in the degree of quaternization on storage. A lesser degree of quaternization produces hydrophobic HTCC polymer that is employed as an efficient vaccine adjuvant to adsorb antigens via hydrogen bonding formed through unoccupied amino groups [40]. Furthermore, Shagdarova et al. (2019) explained that a high degree of quaternization resulted in improved antibacterial action against *E. coli* and *S. epidermis* [41]. The versatile HTCC is widely combined with other chemicals such as poly (N-isopropylacrylamide) carboxylic acid, poly (l-caprolactone) and polyacrylonitrile to improve the solubility, tensile strength, and antimicrobial action for commercial purposes.

2.3. Pyridine Salt Grafted Quaternized Chitosan

Different new QCh-based pyridine salts have been derived that explore synergistic antiviral, antifungal and antibacterial action owing to the attached cationic pyridine salts. In this context, PACS (pyridine chloroacetyl chitosan), BHPACS (4-(5-bromo-2-hydroxybenzylideneamino)-pyridine) and CHPACS (4-(5-chloro-2-hydroxybenzylideneamino)-pyridine) synthetic quaternized chitosan derivatives

have been derived from reacting chloroacetyl chitosan and pyridine. These synthetic QCh-based substances exhibit strong antifungal potency towards *Monilinia fructicola*, *F. oxysporum*, *Cladosporium cucumerinum* and *Colletotrichum legenarium* [42]. The antifungal effect occurred through polycationic-charged pyridine consisting of QCh and negatively charged fungal cell surface. The sturdy electrostatic interaction causes the disorganization and denaturation of proteins present in cell membranes, and ultimately cell death. The literature also reports the synthesis of N-methyl-pyridinium and N-methyl-1, 2, 3-triazolium grafted QCh derivatives that were quite effective for phytopathogenic fungi including *F. wilt*, *Collectotrichum lagenarium* and *F. oxysporum*.

The presence of a pyridine ring and 1, 2, 3-trizolium in the QCh backbone depicted enhanced solubility in alkaline medium and mediated superior antifungal action compared to unmodified chitosan [43]. Jia et al. (2016) synthesized N-(1- carboxbutyl-4-pyridinium) chloride chitosan through introducing nucleophilic substitution on pyridine molecules (Figure 7 [44]. The antifungal activity against *B. cinerea* and *F. fulva* revealed disturbance in cell permeability owing to the adsorbed cationic charges on the fungal cell surface. Consequently, deformation of fungal hypha and cell death was reported [45].

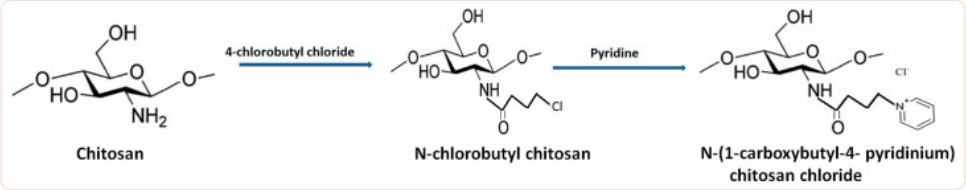

Figure 7

Synthetic route for the development of pyridine-grafted quaternized chitosan.

2.4. Phosphonium Salt Grafted Quaternized Chitosan

Multifunctional quaternary phosphonium salts are organophosphate biocides, basically obtained from the nucleophilic substitution reaction between halide salts and phosphine. These compounds have better antimicrobial action than QCh polymers and are employed in gene therapy, vaccine adjuvant and in water purification units. One of the reported water-soluble quaternary phosphonium salt (WSPCS) has been synthesized from QCh with a minimal degree of quaternization (~4%). The developed WSPCS also exhibited better solubility in organic solvents. Figure 8 illustrates the basic pathway for the synthesis of WSPCS. Increasing the substitution resulted in low cytotoxicity (for mouse fibroblast) and greater antimicrobial action [46]. The cross-linked quaternary-phosphonium chitosan is widely used in wastewater treatment as the phosphonium ion has greater efficiency for the adsorption of chromium ions.

Zeng et al. developed quaternary chitosan phosphonium particles loaded with pEGFP (plasmid type enhanced green fluorescent protein) for the formulation of novel gene vectors. The synthesized particles exhibited biosafety and high potential for gene transfection [47].

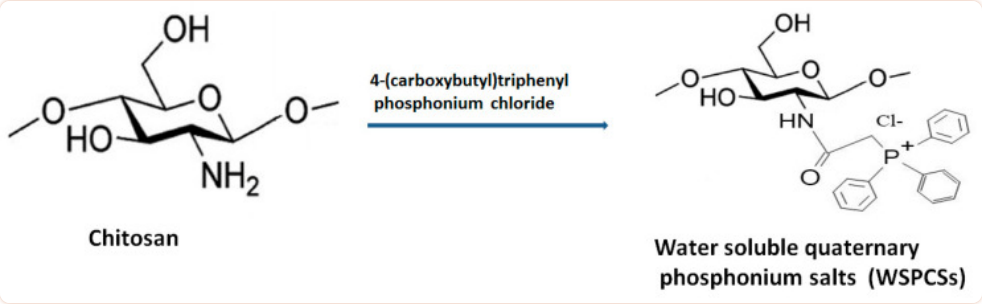

Figure 8

Synthesis of WSPCS from chitosan molecule.

2.5. Other Quaternized Chitosan Derivatives

N-betainates and mono/diquaternary piperazine derivatives of chitosan revealed a varied degree of quaternization without any side reactions. The development of these derivatives provided well-defined structural determinants that are accountable for extreme solubility (4–6% *w*/*v*) at pH = 7 and better absorption/permeation enhancer [48]. Table 2 enlists novel quaternized chitosan derivatives and their biomedical usage.

Table 2

Newly introduced quaternized chitosan derivatives and their biomedical application.

Quaternized Chitosan Derivatives	Biomedical Applications	References
N,N,N-trimethyl-O-(2-hydroxy-3-trimethylammonium propyl) chitosan (TMHTMAPC)	Antimicrobial against *S. aureus* and *E. coli* in both acidic and alkaline pH.	[37,54]
Water soluble N-piperazine chitosan	Pharmaceutical application	[55]
Water soluble N-betainate chitosan	Antibacterial for *S. aureus* and *E. coli* Effect of antibacterial efficacy decreased with increase in amino group substitution.	[48,56]
N,N-dimethyl-O-quaternary ammonium chitosan	Cosmeceuticals (moisturizer), antibacterial	[57]
O-acetyl-chitosan-N-2-hydroxypropyl trimethyl ammonium chloride	Antibacterial (*S. aureus* and *E. coli*), Food preservative	[58]
Amphiphilic 5-(bromo pentyl) trimethyl ammonium conjugated with dodecyl aldehyde chitosan (BPTADDACH)	Efficient drug carrier for hydrophobic candidates	[59]
Diethylaminoethyl-2-N-carboxymethyl-6-O Chitosan (DEAE–CMC) containing vitamin B12 microspheres	Blood compatible drug delivery system	[60]
N,N,N-(diethyl aryl) chitosan chloride	Antifungal/fungicide for crop threatening *Botrytis cinerea.*	[61]
Quaternized N-(aryl) chitosan	Modified antimicrobial action against *E. coli*, *P. aeruginosa*, *S. aureus* and *A. niger* due to presence of phenol hydroxyl group	[62]
Quaternized carboxymethyl chitosan containing guanidine groups (QGCMC)	Food preservative (enhanced shelf life of strawberries), strong bactericidal action in all ranges of pH (acidic, alkaline and neutral)	[63]
O-quaternary ammonium N-acyl thiourea chitosan (OQCATUCS)	*Synergistic antimicrobial action for S. aureus*, *E. coli*, *A. niger*, *P. aeruginosa* and *B. subtilis*	[64]
N,O-[N,N-diethylaminomethyl (diethyl dimethylene ammonium) n] methyl chitosan	Intraocular drug delivery (Enhanced permeability of dexamethasone)	[51,65]
Diethylaminoethyl-2-N-carboxymethyl-6-O Chitosan (DEAE–CMC)		

Rahimi et al. (2019) introduced QC-IMDZ, a novel quaternized chitosan, after grafting quaternary imidazole into the hydroxyl groups of chitosan backbone. Wound dressing material embedded with silver nanocomposite on the QC-IMDZ surface was fabricated that showed superior antimicrobial actions for both bacteria and fungi due to the presence of cationic imidazole. However, excess silver nanocomposite embedded film showed lower solubility and required a prolonged clotting time compared to a low amount silver-nanocomposites-embedded QC-IMDZ films [49].

Another quaternized chitosan derivative 'N-O-[N,N-diethylammoniomethyl (diethyldimethylene ammonium) methyl chitosan has the efficiency to modify the penetration of drug candidates irrespective of their affinity towards mucosal epithelium. Improved drug penetration through porcine buccal epithelium was observed via the paracellular route [50]. Furthermore, ex vivo and in vivo studies suggested satisfactory permeation of dexamethasone in rabbit cornea through the transcellular transport route compared to widely used TMC [51]. Figure 9 summarizes structural and biomedical applications of diverse QCh derivatives synthesized from natural chitosan. Figure 9 compiles a few quaternized chitosan derivatives and their biomedical applications [52,53].

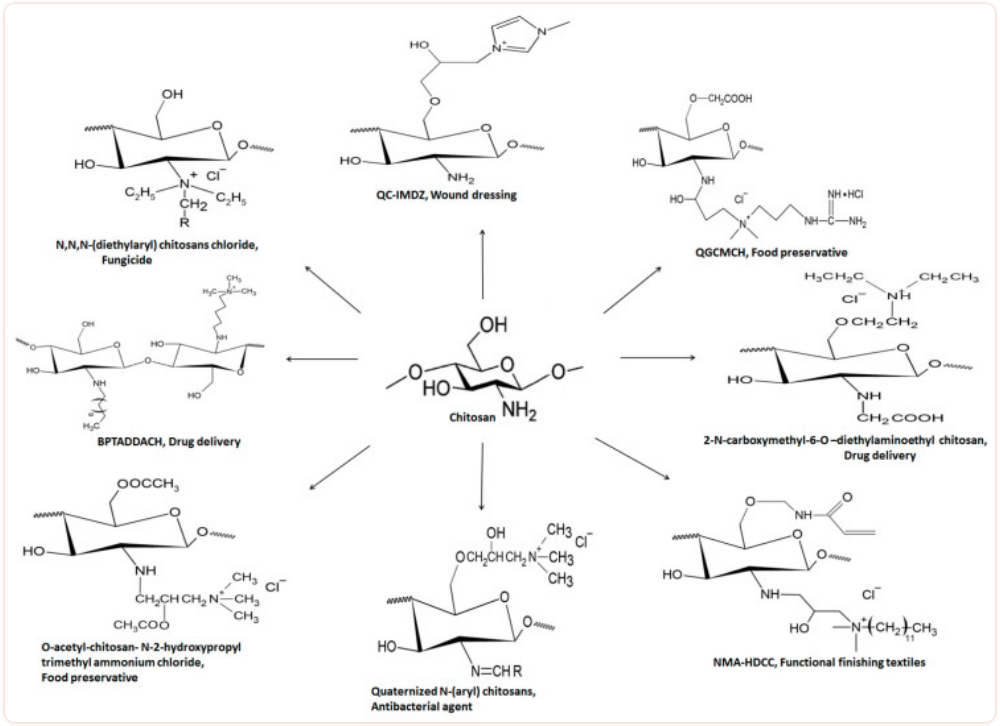

Figure 9

Structural illustration of different QCh derivatives and their biomedical applications.

Wang et al. (2016) developed five aqueous soluble quaternized chitosan derivatives (O-quaternary ammonium salt-chitosan) that contained N-methyl-N-R-N-bis(2-hydroxyethyl) ammonium bromide. Grafted R substituents were benzyl chloride, dodecyl, tetradecyl, hexadecyl and octadecyl. All the O-quaternized derivatives exhibited greater solubility, better antibacterial action for Gram-positive bacteria and lower cytotoxicity against AT2 cell lines. Furthermore, dodecyl- and tetradecyl-grafted O-quaternary ammonium salt chitosan exhibited better biological properties compared to other derivatives and suggested a facile way to design QCh-based hydrogels, membranes, coated beads, scaffolds, dressing materials and bandages and nanoparticles owing to extreme solubility, permanent cationic charges, and characteristic antibacterial actions [67].

Few fatty acids were conjugated on quaternized chitosan nanoparticles for the efficient insulin delivery in liver. Strong electrostatic interaction between positively charged quaternized chitosan and negatively charged insulin was observed. Furthermore, the addition of fatty acids increased the surface hydrophobicity, which mediated hepatocyte absorption, enhanced insulin accumulation in liver cells and illustrated a better antidiabetic effect. Insulin-embedded quaternized chitosan nanoparticles consisting of lauric acid and oleic acid exhibited impressive bioavailability of 233% and 311%, respectively, after subcutaneous administration [68].

3. Biomedical Applications of Quaternized Chitosan Derivatives

3.1. Antimicrobial

The chemical configuration of polycationic QCh is a desirable requisite for the antimicrobial action. Electrostatic interaction between cationic QCh and anionic microorganisms plays an important part for antibacterial activity. A higher degree of substitution of ammonium groups adorned on the backbone of QCh imparts a positive charge that neutralizes cell surfaces of bacteria and disturbs cytoplasmic integrity [37,69]. Moreover, hydrophobic alkyl substitutions on QCh stimulate significant bacterial death as they preferably interact with the inner surface of the bacterial cell wall. The antibacterial effect is prominent in neutral and high pH rather than acidic. The literature envisages that high-molecular-weight and solid QCh derivatives are unable to pass through the cell membrane. They are only adsorbed at the microbial cell surface, channelize electrostatic interactions, hamper nutrient transport, and cause alteration in cell permeability. Conversely, low-molecular-weight water-soluble QCh particles penetrate the bacterial cell wall, intercalate with DNA, and inhibit the transcription process [70]. QCh derivatives always remain positively charged and are soluble at all physiological pH.

The antibacterial activity of the very first N,N,N-trimethyl chitosan was reliant on the degree of quaternization from the [$-N(CH_3)_3$] structure present in the molecule. A higher degree of quaternization improved its aqueous solubility. Additionally, the presence of hydrophobic methyl groups increased the interaction with the lipoidal cell membrane of the microorganism and depicted superior antimicrobial action [71]. Another derivative, N,N-di-ethyl-N-methyl quaternized chitosan (DMCHT) was synthesized via reductive alkylation of aldehydes, through the formation of Schiff base. The developed QCh exhibited antimicrobial efficacy owing to the formation of polyelectrolyte complexes between QCh derivative and peptidoglycan of bacterial cell, which, in turn, inhibited the growth of bacteria [72]. The antimicrobial efficacy of TMC and DMCHT was compared at 50% degree of quaternization. The results showed superior antibacterial activity of TMC against *S. aureus* owing to the presence of smaller alkyl groups that enabled easy interaction with the cell wall of the bacteria. Voluminous DMCHT was comprised of heavy N-ethyl functional groups on its structure [73].

Furthermore, comparative antimicrobial efficiency was assessed among DMCHT (N, N-di-ethyl-N-methyl quaternized chitosan), BZDCHT (N-benzyl-N-N-di methyl chitosan) and BDCHT (N-butyl-N,N-dimethylchitosan) against *S. aureus* and *E. coli* at pH 7.4. The outcomes displayed prominent antimicrobial activity of these QCh as compared to chitosan. DMCHT and BDCHT showed higher hydrophilicity required for better antimicrobial efficacy in comparison to BZCHT. Insertion of hydrophobic groups (phenyl and benzyl) decreased the antimicrobial action by virtue of shielding interaction between N-quaternized site and the cell wall of the bacteria [74]. Reports cite that the protonated amine groups including $+NH_3$ and +ND/+NM (non-quaternized amine group) are highly effective antibacterials compared to +NT (N-trimethylated) ones. However, the chains of TMC derivatives are more flexible and readily interact with the bacterial cells than chitosan at pH ≥ 5.5 suggesting promising antibacterial potential where neutral pH required [75].

Fu et al. (2011) synthesized O, N-quaternized chitosan through attaching benzyl radical on N-quaternized chitosan followed by treatment with ethyl iodide in the presence of alkali at 36 °C. Developed cationic O,N-quaternized chitosan possessed enormous quaternary ammonium chloride moieties that interacted with negative residues of *S. aureus* cell surface. Therefore, affected cell integrity (protein, lipopolysaccharide and techoic acid), altered plasma membrane permeability, leakage of nutrients and mediated cell death [76]. Similar antibacterial action was observed for Gram-negative *E. coli* that contains a thick layer of extracellular lipopolysaccharide and checks the entry of foreign molecules. O-quaternized chitosan exhibited slightly less antibacterial action compared to O,N-quaternized chitosan derivatives by virtue of the reduced electron donation through N-benzyl modification [77,78].

Several natural and synthetic polymers are utilized either alone or in combination for the development of antibacterial systems [79]. In this context, the fabrication of non-woven nanofibers from QCh derivatives; i.e., N-(2-hydroxy)-propyl-3-trimethylammonium salt of chloride has been employed to elaborate wound healing properties of biomaterials including hydrophilicity, water retention capacity, mucoadhesiveness, antimicrobial efficacy, etc. [80]. However, the presence of ionogenic groups in quaternized chitosan generates high repulsive force that limits uniform fabrication of nanofibers via electrospinning. Thus, non-ionic polymers (poly-L-Lactide-co-d and poly vinyl alcohol) are incorporated to make the polymeric solution electrospinnable [81].

3.2. Antiproliferative

Biocompatible quaternized chitosan displays adequate antimicrobial and antiproliferative activity both in vitro and in vivo. For instance, QCh-coated sutures exhibited comparatively high anti-infection and cytocompatibility compared with triclosan-coated sutures, owing to the presence of ample positive charge on decorated quaternary ammonium functional groups that interact with the negatively charged phosphoryl groups of microorganisms [82]. Triclosan, a widely used antibacterial agent, has a significant advantage over other antibiotics by virtue of its low drug resistance and potent inhibition of biofilm formation. However, triclosan-coated sutures are effective in controlling surgical site infections, but the occurrence of tissue toxicity and induction of tumor proliferation and endocrine disorders limit its practice in surgical operation. The above investigation favored the usage of broad spectrum antibacterial QCh as an alternative to triclosan in orthopedic surgery [83].

Yang et al. (2016) elucidated limitations associated with vicryl plus (triclosan coated polyglactin) sutures such as surgical site infections and toxicity. Vicryl plus sutures were modified through surface coating of QC. Bacterial cell adhesion efficiency of modified HV sutures against *Staphylococcus epidermidis* and *S. aureus* revealed significant antibacterial efficiency for both pathogens for 48 h. Furthermore, the HV sutures were found to be cytocompatible with human-skin-derived fibroblast cells. The procedural flexibility and economic value of QCh-modified HV sutures laid down a suitable strategy to manage suture-related infections in orthopedic surgeries [84,85].

Furthermore, Li et al. (2018) focused on the clinical application of QCh in malignant melanoma (B-Raf^{V600E}), one of the most invasive skin carcinomas. Human melanoma cells were interacted individually with vermurafenib (B-Raf^{V600E} inhibitor), QCh and a combination of both, to investigate cell permeability, proliferation, apoptosis, and viability. The outcomes revealed that the presence of QCh promoted an antiproliferative effect against melanoma cells. Moreover, QCh could enhance cell permeability at the preliminary stage, thus facilitating intracellular drug uptake. Interestingly, polycationic QCh made electrostatic interactions with negatively charged cancerous cells that disturbed their cytoplasmic integrity. The investigation concluded that QCh upset the surface charges on melanoma cell, which may be an important parameter to change cell permeability [86]. Wongwanakul et al. (2017) examined cell proliferation and cell differentiation properties of QCh on the intestinal barrier through CaCo-2 cell lines in vitro model. Poor cytotoxicity and superior biocompatibility on the intestinal barrier were observed from a lesser degree of substitution and low dose of QCh. The study suggested potential usage of QCH in designing oral drug delivery system [87].

3.3. Antibiofilm

Biofilms, the complex colonies of living microorganisms developed at the infection site, are extremely resistant to antibiotics and antimicrobials. These biofilms consist of a well-recognized self-produced extracellular matrix made up of protein, polysaccharide, and DNA [88]. Bacterial adherence and the biofilm formation at the implantation site involve two typical processes. Initially, the accumulation of microbial community starts, which releases polysaccharide intracellular adhesion, an extracellular substance. Furthermore, PIA is mediated through intracellular adhesion that comprised of different core genes such as ica A, B, C, ica D and one regulatory gene icaR. The icaA gene is an index of biofilm preparation. A high concentration of QCh is capable of preventing icaA transcription, thus limiting biofilm formation or microbial viability [89].

Biofilms produced at the post-surgical infection sites are mostly associated with the use of medical devices including catheters, implants, endotracheal tubes, valves, etc. Both Gram-positive (*S. aureus*, *S. epidermis*) and Gram-negative (*P. aeruginosa*) bacterial communities grow on healthcare devices [90]. These pathogenic bacteria can survive even in the presence of high doses of antibiotics (1000 times high) than required to eliminate their planktonic population. Once well-organized biofilm is formed around the surgical implants surface, it becomes difficult to completely rule out through antibiotic therapy [91].

Most of the existing antibiotics and antimicrobials are unable to eradicate biofilms, owing to their similar activity spectrum and common modes of action. QCh can be employed for the elimination of biofilm by virtue of its anti-infective property against bacteria, viruses, and fungi [77,92]. Both high- and low-molecular-weight QCh functionalized with hydrophobic residues (thiol protected 6-mercaptonicotinamide and methylated cyclodextrins) are reported as unconventional antimicrobial agents as they display improved wound healing, mucoadhesiveness and antibiofilm potential [93].

Piras et al. (2019) proved the biomedical application of QCh to be possible, i.e., antibacterial, anti-adhesive and antibiofilm. They demonstrated collective data of high- and low-molecular-weight QCh and their efficacy against common pathogens including *P. aeruginosa* and *S. epidermis*. Low-molecular-weight QCh derivatives were efficacious biofilm eliminators at very low concentrations, whereas high-molecular-weight QCh after covalent immobilization on titanium plates could be applied as spray or liquid plasters for the inhibition of bacterial adhesion. Thus, QCh-modified titanium implants mediated the dynamic strategy to terminate biofilm associated with medical devices [94].

3.4. Antifungal Activity

As with antibacterial activity, the occurrence of ample positive charge on QCh supposed to interact with the anionic residues of macromolecules present on the fungal surface resulted in the leakage of intracellular electrolytes and nutrients. Reports cite that QCh affects morphogenesis of the fungal cell wall and controls the functions of enzymes accountable for growth [95]. Guo et al. (2007) synthesized different QCh derivatives for the study of antifungal activity against *Botrytis cinerea* and *Colletotrichum lagenarium*. Four QCh derivatives, i.e., N-(2-hydroxyl-phenyl)-N,N-dimethyl CS, N-(5-bromic-2-hydroxyl-phenyl)-N,N-dimethyl CS, N-(2-hydroxyl-5-nitrophenyl)N,N-dimethtyl CS and N-(5-chloro-2-hydroxy-phenyl)-N,N-dimethyl CS, were developed, which exhibited better antifungal effects compared to the unmodified chitosan [96]. The result emphasized that high molecularity of QCh is accountable for stronger antifungal efficacy [97].

Insertion of an arylfurfural group to the N-quaternized chitosan indicated amplified antifungal effects compared to unmodified chitosan. Moreover, N-quaternized arylfuran chitosan (QACHT) substituted with chlorine and nitrogen oxide further modified the antimicrobial and the antifungal effects that interacted with anionic macromolecules of fungal cell wall and mediating seepage of intracellular electrolytes [98]. Deacetylated chitosan functionalized with propyl and pentyl trimethylammonium bromide exhibited increased antifungal activity, i.e., three- and six-fold higher for *A. flavus*. In vitro antifungal assay evaluated the minimum inhibitory concentration for 72 h by varying the QCh derivatives concentration (0.5–16 g/L). The outcomes revealed that QCh derivatives inhibited mycelium growth even at one quarter of the concentration of deacetylated chitosan [99].

The antifungal activity of QCh can also be improved by the addition of more quaternary ammonium groups such as N-trimethyl. Increased molecular weight, positive charge, degree of quaternization and hydrophobic functional moieties intensify antifungal action. Il'ina et al. (2017) synthesized synthetic metal (Cu II) complexes of QCh (N-propyl chitosan derivative) and evaluated the antifungal efficacy against yeast (*C. albicans* and *R. rubra*) and mycelial fungi (*F. oxysporum* and *C. herbarum*). N-propyl-derived QCh was developed through treatment with glycidyl trimethyl ammonium chloride under controlled conditions. Amalgamation of N-propyl QCh (53%) and copper ions (13%) proved efficient against common fungal plant pathogen *F. oxysporum* [100]. Viegas de Souza et al. (2017) synthesized low-molecular-weight QCh derivative (dodecyl aldehyde-treated propyl trimethyl-ammonium bromide chitosan) to investigate the antifungal effect on *A. parasiticus* and *A. flavus*. The outcomes revealed that amphiphilic QCh derivatives exhibited amplified inhibition indices that were reliant on hydrophobicity and polymer concentrations. These QCh derivatives opened novel avenues for the development of chitosan-based biofungicides [101].

3.5. Mucoadhesiveness

N,N,N-trimethyl chitosan is widely utilized as a penetration enhancer for the delivery of peptides and macromolecular compounds across the mucosa in alkaline and neutral pH medium. Here, the degree of quaternization has a direct impact on the property of mucoadhesiveness and penetration across the membrane. Snyman et al. (2003) studied the effect of extent of quaternization (22–48%) and molecular mass (100,000 g/mole) on the biological activity of synthesized TMC polymers. The outcomes suggested decreased mucoadhesiveness on increased quaternization of TMC polymers [35,102].

The ocular or ophthalmic drug delivery system encounters several route barriers related to nasolacrimal drainage, stimulated lacrimation, blinking, blood ocular barrier and corneal impermeability. The use of mucoadhesive polymers such as chitosan derivatives facilitates effective ocular drug delivery owing to their elite interaction with the mucosal membrane. The presence of positive charge mediates the electrostatic interaction with the anionic mucin of the mucosal layer [103]. The ocular drug absorption of therapeutics depends on their aqueous solubility and mucoadhesiveness. Quaternized chitosan shows better candidature for enhanced permeation across ophthalmic tissues owing to their improved solubility and mucoadhesive property. However, beta-cyclodextrin conjugated chitosan has been employed for the ocular delivery of dexamethasone but restricted mucoadhesive limited their use.

Piras et al. (2018) demonstrated the development of methyl-beta-cyclodextrin grafted quaternary ammonium chitosan that was processed through treatment with hexamethylene diisocyanate. The QCh derivative efficiently carried dexamethasone, exhibited drastic changes in solubility and bioavailability. Moreover, a stable, mucoadhesive and controlled release formulation could be achieved. Preliminary assessments revealed that the developed conjugate has promising potential for the effective management of ocular disorders [93]. Yostawonkul et al. (2017) developed mucoadhesive oleoyl- quaternized chitosan-coated nanostructured lipid carriers

(NLCs). Alpha-mangostin, a hydrophobic drug was embedded in the developed NLC, which exhibited more than 90% entrapment efficiency and minimum polydispersity. Excellent mucoadhesive, higher physical stability and greater cytotoxicity were observed against cancerous Caco-2 cells over Hela cells [104].

Konovalova et al. (2018) analyzed the comparative mucoadhesive property of chitosan (20 kDa) and its hydrophobic and quaternized hydrophobic chitosan derivatives (HC and QHC). The unmodified chitosan exhibited large aggregates in the keratinocytes and colon cells of murine small intestine, whereas HC and QHC showed mucoadhesiveness as a fine dotted line when observed through confocal microscopy [105]. Hydrophobic derivatives of chitosan mediated local drug release and improved biodegradation.

3.6. Drug Carriers

3.6.1. Nanofibers

Nanofibers have always been a lucrative tool for the preparation of scaffolds, either as topically applied dressing material or in the membrane unit for filtration. Water purification systems enclosing membrane filtration units are widely accepted strategies for the retention of pathogens including bacteria and viruses according to their size. Table 3 compiles few novel biomedical usages of QCh-based nanofibers. Reports cite that holding small-sized viruses (<25 nm) necessitates enormous membrane surface area along with low water flux and high transmembrane pressure. Moreover, the filtration membrane unit has to be replaced with another new membrane frequently. To overcome this downside, Bai et al. (2013) fabricated an electro spun nanofibrous membrane comprised of quaternized chitosan polymer (HTCC) and graphene allotrope. HTCC has the proficiency to adsorb pathogenic non-enveloped porcine parvovirus on its surface. Distinctive attributes of graphene hydrophobicity and ionogenic HTCC enhanced the functional efficiency of developed nanofibers (95% virus retention). The developed nanofibers embedded with a blend of HTCC/graphene depicted effective microfiltration membrane water purification systems featured with low pressure technology for the significant removal of pathogens [106].

Table 3

Quaternized chitosan-embedded nanofibers in diverse biomedical arena.

Components	Purpose	Research Outcomes	References
HTCC and PVA	Retention of non-enveloped virus on the highly charged HTCC/PVA nanofibers.	Nano-scaled HTCC/PVA nanofibers (100–200 nm) were developed, having the potential to adsorb mammalian virus porcine parvovirus (95%). The developed system followed Freundlich isotherm and showed fast adsorption kinetics (pseudo first order), which suggested the formation of efficient filter material for the purification of water	[110]
Doxorubicin, poly (L-lactide-coD, L-lactide) and QCh	Doxorubicin embedded poly (L-lactide-coD, L-lactide) mats were modified with QCh to enhance anti-proliferative activity.	Developed mats were evaluated against human breast carcinoma cell lines (MCF-7) and exhibited reduced cell viability and amplified antiproliferative activity. Fluorescent microscopy revealed that the presence of QCh induced apoptosis, which was the primary mechanism of MCF-7 cell death.	[111]
2,3-Epoxy-propyl trimethyl ammonium chloride	QCh fibres were designed using 2,3-epoxypropyl trimethyl. Ammonium chloride following ring open reaction to modify antibacterial and liquid absorption capacity.	Outcomes revealed excellent water retention capacity, modified swelling index and mechanical strength compared to bare chitosan. Superior antibacterial efficacy against *S. aureus* and lower cytotoxicity suggested its vital role in fabricating wound dressing materials.	[112]
Poly (lactic acid), QCh	Stereo complex crystallite (SC) membrane containing poly (lactic acid) QCh were employed to design disinfectant wound dressing material.	The enhanced thermal and mechanical properties of developed SC membrane owing to restricted mobility of lactide chains. They have better wound healing capacity (100% in 15 days). This biomass-based membrane was multifunctional as it has antioxidant, antibacterial and wound healing	[113]

Santos et al. (2018) extended the study and fabricated antibacterial nanofibers from a blend of N-(2-hydroxy)-propyl-3-trimethylammonium chitosan chloride (QCh) and polycaprolactone (PCL) polymeric solutions. The produced nanofibers displayed improved hydrophilicity and tissue compatibility with superior mechanical strength when evaluated for enzymatic degradation, cell adhesion, and cytotoxicity against neonatal human dermal fibroblasts cells. The viscosity and degree of deacetylation of QCh strongly affected the alignment of nanofibers that was required for relative orientation with cancerous cells for better cytotoxic activity. The fabricated QCh/PCL nanofibers possessed essential benchmarks required for designing wound dressing materials in the domain of tissue engineering [107].

Amplified antimicrobial efficiency of quaternized chitosan was exploited by Cheah et al. (2019) as they performed surface grafting of PAN nanofibers (P-CN) with quarternary amine (glycidyl trimethyl ammonium chloride) functionalized chitosan under acidic, neutral, and alkaline conditions. Developed water-stable quaternized chitosan nanofibrous membranes (P-HTCC) were subjected for evaluation of antibacterial activity against *E. coli*. The outcomes from the microbiological assessment revealed that the quaternized chitosan-derived membrane developed in acidic medium exhibited stronger antibacterial action (99.95% for *E. coli*) compared to the neutral and alkaline medium. The fabricated P-HTCC membranes had the potential to be assembled into a microfiltration unit for the disinfection of Gram-negative pathogen *E. coli* [108].

Mi et al. (2014) addressed the issue of unsafe drinking water containing countless microbial loads and toxic impurities accountable for millions of deaths every year. An economical antiviral filtration material was fabricated utilizing ionogenic quaternized chitosan (HTCC) and non-ionogenic polyvinyl alcohol (PVA). The electrospun material embraced the high surface area required for effective water adsorption. Furthermore, HTCC/PVA nanofibers were treated with glutaraldehyde (cross linking agent) to control the water solubility and enhance the water stability (only 30% swelling in 6 h). The system could retain both enveloped and non-enveloped viruses. The HTCC-/PVA-embedded microfiltration membrane was affordable and proved to be an efficient low-pressure filtration unit by virtue of significant retention of pathogens [109].

3.6.2. Hydrogel Hydrogels have a cross-linked network of variable hydrophilic functional groups containing polymers that can absorb plentiful water. Surface-adorned hydrophilic groups such as amine ($-NH_2$), hydroxyl (−OH), sulphate ($-SO_3H$), and amide (−CONH−) empower hydrogel to absorb watery fluid that expands their volume due to swelling. Hydrogel-based dressing materials provide several advantages, including ample absorption of tissue exudate, maintenance of optimum moisture content at the site and encouraging cell proliferation (Table 4). Antibacterial hydrogels are highly required in the health care sector to accelerate the wound healing cure rate. In this context, Xiao et al. (2020) prepared hydrogel consisting of QCh, chemical cross-linker ‘polyacrylamide’, and silver nanoparticles. The developed hydrogel exhibited desirable tensile strength (approximately 100 kPa) with a shear stress of 10^4 Pa. Excellent swelling capacity, a synergistic antibacterial effect, and low toxicity of Ag-mediated hydrogel reinforced the designing of appropriate wound dressing materials [115].

Table 4

Biomedical utility of QCh-derived hydrogels.

Objective	Components	Research Highlights	References
Multifunctional QCh-based polyacrylamide hydrogel was developed that contained hemostatic and skin adhesive properties	QCh, Matrigel-polyacrylamide	The developed hybrid hydrogel had a three-dimensional microporous integrity and exhibited high mechanical strength and good adhesiveness with low toxicity. The outcomes from the histology study demonstrated improvement in wound healing, collagen deposition, and stimulation of skin adnexal regeneration. The developed QCh-based antibacterial hydrogel demonstrated promising potential for designing wound dressing materials.	[118]
Dual crosslinked QCh-clindamycin loaded hydrogel was prepared to manage methicillin-resistant *S. aureus* (MRSA) bacteria	QCh, clindamycin	The developed nanocomposite-embedded hydrogel withstood sufficient mechanical and injectable efficiencies. The system responded on variable pH that enabled maximum interaction with MRSA bacteria (90% killed) in acidic conditions and overcame the antibiotic resistance challenge.	[119]
A novel wound dressing-based injectable hydrogel was designed employing QCh and PLEL (PLEL-nBG-QCS-C) hydrogel to promote angiogenesis.	QCh and PLEL [Poly (D, L-lactide)-poly (ethylene glycol)-poly (D,L-lactide)] and bioactive glass	PLEL hydrogels preloaded with bioactive glass (CaO-SiO_2-P_2O_5) could efficiently seal the broken skin and increase the cure rate of wounds. Additionally, they were thermosensitive, tissue adhesive, and antibacterial.	[120]
		The developed transparent thermosensitive hydrogel presented desirable porosity	

You et al. (2016) synthesized quaternized chitosan via reaction of chitosan with 3-chloro-2-hydroxypropyltrimethylammonium chloride in an alkaline solution. Thereafter, the polyelectrolyte complex hydrogel was prepared through in situ polymerization of poly acrylic acid monomers in quaternized chitosan solution. Resultant elastic, mechanically strong and surface tunable hydrogel was developed that displayed superb solvent-induced shape memory performance [116].

Mamidi et al. (2021) demonstrated a pH- and thermal-responsive chitosan-based nanocomposite (CNP) hydrogel that has potential applications in nanomedicine and nanotechnology. They developed an integrated chitosan nanocomposite containing poly (N(4-aminophenyl) methacrylamide)- carbon and diclofenac. The system possessed several conductive physicochemical properties such as spherical shape and uniform particle size. Additionally, the CNPs were pH- and heat-sensitive and exhibited controlled release for 15 days. Moreover, the designed CNP showed significant cell viability for human fibroblast cells [117].

3.6.3. Beads Thermoduric bacteria that can survive even after pasteurization of milk pose momentous threat to dairy and beverages industries. To overcome this challenge, biodegradable HTCC-anchored magnetic cellulose beads were developed via the dropping technique which could resist temperature up to 300 °C. Extended antibacterial efficacy against *Alicyclobacillus acidoterrestris* suggested the potential application of developed beads for food safety management [125]. Furthermore, quaternized chitosan beads were developed to adsorb phosphate and nitrate ions present in aqueous solution. Quaternized chitosan beads were formulated through reacting cross-linked chitosan with trimethyl ammonium chloride. The quaternized chitosan beads were quite effective in the pH range of 3–9 and exhibited an adsorption capacity for phosphate (97.5%) and nitrate ions (99%) that followed Freundlich isotherm model. The presence of common ions such as chloride, sulphate and bicarbonate did not alter the sorption capacity of quaternized chitosan beads [126].

The literature envisages that polycationic ammoniated polymers are fascinating options for the adsorption of negatively charged ions and sulphated polysaccharides through electrostatic interaction. In this regard, QCh has been explored for capturing anions, even at high pH. Eskandarloo et al. (2018) proposed the formulation of quaternized chitosan/polystyrene microbeads (CS/PS) for the selective adsorption of heparin, an anticoagulant from porcine intestinal mucosa sample. The comparative adsorption efficiency of CS/PS microbeads and marketed Amberlite FPA98 Cl resin was evaluated utilizing a heparin-bovine serum albumin model in pH range 4.1–9.2. The outcomes depicted superior adsorption efficiency of CS/PS micro beads (2.84 mg/g) and could be regenerated after treating with sodium chloride solution. Furthermore, the recovered microbeads can be reused for adsorption of heparin without any loss of adsorption capacity. Moreover, CS/PS microbeads could adsorb heparin from real biological sample containing heparin [127].

Quinlan et al. (2016) utilized quaternized chitosan hydrogel beads for efficient adsorption of 2-naphthoxyacetic acid from oil sand processed water (OSPW) system. 2-naphthoxyacetic acid is highly toxic and occurs in significant concentrations (40–70 mg/L) in OSPW that requires prolonged time for degradation. Hence, it necessitates removal of 2-naphthoxyacetic acid through either filtration, advanced oxidation, or adsorption methods. QCh has been identified as an attractive adsorbent by virtue of adsorption of an-

ionic ions. The research emphasized retention of aromatic organic carboxylate site present in 2-naphthoxyacetic acid through polycationic QCh via the ion exchange adsorption process. The mode of adsorption signified Langmuir isotherm following pseudo first-order kinetics. The developed QCh hydrogel beads were moderately swellable and demonstrated effective adsorption of 2-naphthoxyacetic acid (91%) at the initial concentration of 200 mg/mL [128].

3.6.4. Nanoparticles Splendid accomplishments have been anticipated through chitosan-based nanoparticles for the management of different diseases over past decade. These biodegradable and biocompatible nanoparticles are not only exhibit improved solubility, site specific/localized action but also minimize undesirable toxicity. Highly demanded chitosan is frequently explored as a carrier in drug delivery systems, fabrication of wound dressing materials, management of skin regeneration and tissue engineering. Quaternized chitosan-based nanoparticles (QCh NPs) have attracted wide interest owing to their exclusive physicochemical and biological features. Chemical modification such as grafting, functionalization, Schiff base formation and quaternization are few strategies that expand physicochemical and biological features of chitosan. Quaternization of chitosan significantly improves the aqueous solubility in neutral pH hence enhances the diffusion of drug moiety across biological membrane in neutral/alkaline physiological conditions. The positive charge facilitates pronounced mucoadhesiveness, antimicrobial activity, biocompatibility, and biodegradability as well as widening its biomedical applications. Numerous trimethyl, triethyl, dimethyl ethyl, and N-(2-hydroxy-3 trimethyl ammonium) propyl derivatives of quaternized chitosans have been discussed in Table 5 as potential carriers for the transportation of proteins, genes, vaccines, and chemotherapeutics at the target site [39,129].

Table 5

QCh-based nanoparticles and their biomedical applications.

Objective	Components	Research Highlights	References
Ketoconazole was entrapped in QCh NPs for superior antifungal activity	Ketoconazole, QCh, sodium triphosphate	Nanoscaled KCZ-QCSNPs displayed superb entrapment efficiency (~90%). Performed tube dilution method revealed preeminent antimicrobial activity.	[134]
QCh derivative 'HTCC' NPs were embedded in various fabric materials to evaluate antimicrobial efficacy.	HTCC, cotton fabric, polyester, polyacrylic acid	The developed HTCC nanoparticles embedded in cotton fabric exhibited superior antimicrobial action against *Fusarium oxysporum* and *Bacillus subtilis* compared to polyester and mixture of cotton.	[135]
Anthrax vaccine adjuvant containing Fucoidan-HTCC nanoparticles were developed to improve rapid induction of immunity	Sulphated polysaccharide (Fucoidan, FUC) and HTCC	An active complexation between opposite-charged FUC and HTCC was conducted through varying their mass ratio. MTT assay on L929 or JAWS dendritic cells evaluated low cytotoxicity, improved cellular internalization and high cell viability. Combination of FUC-HTCCNPs and anthrax vaccine adsorbed (AVA) significantly improved magnitude of cellular/humoral immunity and mice survival rate compared to administration of AVA alone.	[136]
Nanoparticles containing N-2-HTCC and N,O-CMC encapsulated vaccine antigens (IBV/H120) were developed for significant	N-2-HTCC, N,O-carboxy methyl chitosan (CMC), infectious bronchitis virus (IBV) (H120 and Newcastle disease virus	The developed nanoparticles, i.e., N-2-HTCC-CMC/NDV/IBV, predicted great stability and low cytotoxicity on storing at 37 °C for 3 weeks. In vivo assay on chicken revealed sustained release of both NDV and IBV with enhanced release of IgG and IgA that	[137]

3.6.5. Quaternized Chitosan Nanocomposites Strong interaction between bifunctional quaternized chitosan and carbon nanocomposite displayed superior mechanical properties (tensile strength), improved ionic absorption, enhanced antimicrobial action owing to their enormous surface-to-volume ratio (surface area), smaller size, and higher dispersion in given media. Abdel-Aziz et al. (2020) have developed a novel antituberculosis delivery system composed of N,N,N-trimethyl chloride (TMC)/Ag nanocomposite synthesized through a one pot green route. Synthesized nanocomposite (11–17 nm) system has exhibited promising antimycobacterial action (MIC 1.95 µg/mL). The observed antitumor activity displayed less toxicity (IC_{50} 357.2 µg/mL) for normal (WI 38) lung cells and preeminent growth inhibition for A549 cancerous cells (IC_{50} 12.3 µg/mL) [130]. Luo et al. (2015) initially synthesized nanocomposites from chitosan/montmorillonite resin and quaternized modifier 2,3-epoxypropyltrimethyl ammonium chloride chitosan/montmorillonite resin. The developed quaternized chitosan-containing nanocomposites were small, spherical, smooth, dense, and exhibiting good dispersibility in water. The adsorption study performed on methyl orange revealed that quaternized chitosan/montmorillonite was strongly adsorbed compared to without montmorillonite, and thus can be a prospective material for column packing and wastewater treatment [131]. In this series, mechanical and ionic conductive properties of QCH functionalized carbon nanotube membrane matrix were evaluated. Improved dispersion of carbon nanotube promoted the load transfer and assisted hydroxide ion exchange through the membrane matrix. Reduced ionic conductivity and modified tensile strength indicated the potential application in preparation of anionic exchange membrane fuel cells [132]. Similarly, Gong et al. (2019) developed a layered double hydroxide ion conductor composed of QCH/PVA and carbon nanotubes. The system exhibited 1.57-fold enhanced tensile strength, 47 mS/cm^2 ionic conductivity at 80 °C, and displayed a good reinforcing property [133].

QCh nanoparticles are highly acclaimed for designing oral drug delivery systems by virtue of significant drug diffusion and improved penetration across the epithelial barrier. Several ‘bottom up’ methods for nanoparticles development are widely emphasized, including emulsion droplet coalescence, ionic gelation, the reverse micelle method, self-assembly, chemical alteration, coacervation, and precipitation. Methods such as milling, ultrasonication, and high-pressure homogenization listed as ‘top down’ are also employed for nanoparticles synthesis [140]. Omar et al. (2021) developed novel oral drug nanocarriers composed of quaternized aminated chitosan and curcumin to enable the slow release of curcumin at the site of colon.

The ionic gelation method was opted for to formulate nanoparticles (Q-AmCs NPs) employing different concentration of crosslinker ‘sodium triphosphate’. Formulated Q-AmCs NPs were comparatively nanoscaled (~162 nm) with higher entrapment efficiency (~94.4%) and maximum potential of +48.3 mV than aminated chitosan (~231 nm, 75%, +32.8 mV). The in vitro drug release study in various physiological media (simulate gastric fluid, pH = 1.2; and simulated colon fluid, pH = 7.4) exhibited controlled cumulative drug release in alkaline pH (74%). The NPs depicted acceptable biocompatibility and biodegradability that suggested potential use for cancer management [141]. Improved solubility of quaternized chitosan in variable pH ranges encourages versatile biomedical usage [142]. Advanced applications of quaternized chitosan NPs are reported in vaccine development as well. The occurrence of

cationic charge on quaternary ammonium groups is independent of any pH of surrounding media. Moreover, the positive charge facilitates advanced bioadhesion and drug delivery across mucosal membrane via strong electrostatic interaction with negatively charged endothelial regions [143].

3.6.6. Vaccine Adjuvants Vaccine adjuvants are essential components that modify vaccine potency through encouraging cell-mediated or humoral immune responses via vaccine antigens. An ideal adjuvant should have the efficacy to solubilize antigens, facilitate transportation across mucosal barrier and potential for encouraging systemic and mucosal immunity. Chitosan and chitosan derivatives are fascinating candidates for vaccine adjuvants by virtue of their remarkable physicochemical (solubility, stability, biodegradability) and biological values (cytocompatibility, non-toxicity, antimicrobial). Reports cited that quaternized chitosan have greater potential to induce antigen-presenting cells (APCs), encourage cytokine stimulation and produce preferred humoral, cellular, and mucosal immune responses [144].

A lot of chemical structure modifications have been performed with the primary amine group of chitosan to enable it to have high aqueous solubility without altering exclusive biological properties. QCh decorated with N, O-carboxymethyl and N-2-hydroxypropyl trimethyl functional moieties are frequently preferred for the synthesis of vaccine adjuvants. During vaccine preparation, the pH of QCh ranges from 4.3 to 5.5, which facilitates protonation of chitosan and makes natural electrostatic interaction with negatively charged encapsulated antigen [145]. QCh and its derivatives are utilized as potential mucosal vaccine adjuvants owing to their biological features including the formation of natural electrostatic interaction between cationic chitosan and anionic sialic acid in mucus that assists improved mucosal absorption of antigen. TMC possesses all these virtues along with higher aqueous solubility, greater mucoadhesiveness and more stability in diverse ionic conditions than chitosan; hence, it is utilized broadly in vaccine development. Moreover, TMC finds vital role in vaccine development because of its similar functional performance as that of synthetic adjuvants including alum, cyclic guanosine monophosphate and Freund's adjuvant, etc. [146]. Moreover, QCh has a better capacity to open tight mucosa junctions than chitosan, which facilitate permeability of antigens within the mucosal cells [147]. Biocompatible, non-reactogenic, economical and biodegradable QCh are also reported for their immunomodulation ability [148].

Recently, many novel vaccine adjuvants have been engineered for the modification of adaptive immune responses to deliver antigen in the body that enhance the potency and maintain immunity for a long duration. Alum has been the sole vaccine adjuvant approved for human use but limits significant stimulation of cell-mediated immune responses. In this context, Tao et al. (2017) evaluated immune-modifying features of N-(2-hydroxy) propyl-3-trimethylammonium chitosan chloride (HTCC) as a vaccine adjuvant for HEV (hepatitis E virus). HTCC showed strong immune-modifying effects when co-administered with HEV recombinant polypeptide inoculum via intramuscular way. The outcomes revealed enhanced serum HE-recognized IgG antibodies, amplified CD4+, $CD8^-$ T lymphocytes, proliferation of splenocytes, and growths of IFN-γ-secreting T helper cells in peripheral blood after vaccination [149]. Hence, HTCC adjuvant has the potential to induce significant antibody responses via stimulating Th-1 and Th-2 cells, cytotoxic T cells and macrophages that initiate typical mechanisms of the host defense process [150]. Th-1 cells are associated with protection against in-

tracellular pathogens and encourage delayed-type hypersensitivity reactions, whereas Th-2 cells encounter extracellular pathogens and mediate humoral responses. Figure 10 illustrates the development of immunity after the administration of mucoadhesive QCH-based vaccine adjuvant [151].

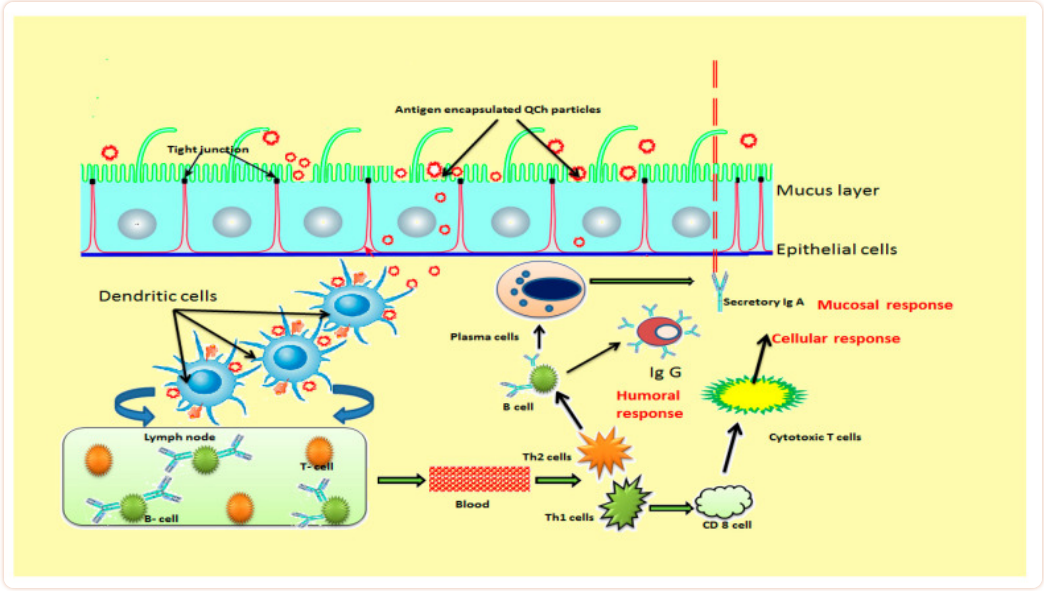

Figure 10

Schematic illustration of immunity development after administration of mucoadhesive QCh-based vaccine adjuvant.

Wu et al. (2012) extended the study and demonstrated safe usage of HTCC supported hydrogel for efficient nasal immunization. A novel thermosensitive hydrogel was developed utilizing α, β-glycerophosphate and different quaternized degree having HTCC (QD 41%, 60%, 79%, 99%). The developed adjuvant was linked with Zaire Ebola virus glycoprotein antigen and evaluated for intranasal vaccine delivery efficacy. HTCC with moderate quaternization (60% and 79%) induced high immune-modulating effects and extensively released IgG-G1-G2a antibodies in serum and IgA in lungs, probably due to prolonged resistance due to the thermosensitive nature of hydrogel. Furthermore, HTCC mediated the higher release of IFN-γ and interleukins (IL-2, IL-10, IL-4), and Th1 and Th2 cells displayed enhanced cellular immune responses [151,152].

Wang et al. (2016) developed quaternized chitosan-based microgel adjuvant for H_5N_1 spilt vaccine. Microgels were prepared through the premix membrane emulsification method without the addition of a chemical crosslinker. The formed polycationic QCh microgels were smaller (807 nm), pH-sensitive, biocompatible, and capable of enhancing both cellular/humoral immunity. Microgels containing QCh with a moderate degree of quaternization (41% and 60%) exhibited favorable immune responses at lower doses when investigated against bone-marrow-derived dendritic cells [153]. Traditional immunization techniques including subcutaneous and intramuscular administration can provoke systemic immunoresponses. These approaches are unable to evoke resilient local immunity, specifically in the mucosal region, the first line of defense against pathogens [154].

The nasopharynx lymphoid tissues cannot support strong mucosal immunity or immune responses. While antigen or foreign particles enter on the nasal mucosal surface, antigen presenting cells on epithelial cells identify and present them to macrophages or lymphocytes that cause their differentiation, activation, and proliferation. Non-adherent antigens are not entertained by the tightly bound epithelial cells, so they produce poor immunogenicity [155]. To overcome the above downside, Zhang et al. (2018) developed curdlan sulphate complexed O-HTCC nanoparticles adjuvant to improve immunogenicity of antigen ovalbumin (Ova) through intranasal vaccination. Soluble curdlan sulphate is an extracellular polysaccharide that particularly identifies the dectin1 receptor on immune cell surfaces. Reports cited that curdlan sulphate elicited satisfactory cellular or humoral responses. However, being anionic in nature, it is hardly adsorbed over nose epithelial cells that limit its application in mucosal immunotherapy. Hence, polycationic, immunogenic O-HTCC was chosen to make complex with negatively charged curdlan sulphate (CS) followed by entrapment of antigen ovalbumin (Ova). An efficient Ova-loaded vaccine adjuvant (Ova/CS/O-HTCC) was developed under mild conditions. When administered through nasal mucosa dripping in BALB/c mice (Bagg albino laboratory bred strain), adjuvant Ova/CS/O-HTCC activated APCs and enhanced both cellular and humoral activity of Ova. The adjuvant also ameliorated Th-2 cells responses and reduced allergic reactions [156].

Nevagi et al. (2018) developed an efficient self-adjuvating TMC-peptide vaccine based on ionic interaction between cationic TMC and anionic alpha-poly- (l-glutamic acid) peptide antigen. The designed system induced higher systemic and mucosal antibodies compared to the reference cholera toxin B, a mucosal adjuvant conjugated with TMC. A self-adjuvant evident reduction in bacterial burden in nasal secretions of immunized mice was thus found to be effective for group A *Streptococcus* pathogen [157].

4. Miscellaneous

4.1. Orthopedic Surgery

Biomaterial-related infections are serious glitches in orthopedic surgery. The application of antibiotics either locally or given systemically has proven valuable in clinical research. Bone cements are applied to deliver antibiotics locally in high doses without triggering systemic toxicity. However, at a high level, these antibiotics may reduce the osteoblasts cell viability, proliferation, and alkaline phosphatase action that hinders physiological functions of bone marrow mesenchymal cells, resulting in compromised bone healing process. To overcome the above issue, quaternized chitosan derivative 'hydroxy-propyl-trimethyl ammonium chloride chitosan (HACC)' loaded on polymethylmethacrylate (PMMA) bone cement was investigated to resolve the formed biofilm on the surface of bone cement. HACC-functionalized PMMA bone cement exhibited better antibacterial action compared to control against versatile clinically isolated microbes including *S. epidermidis 389*, methicillin-resistant *S. epidermidis* and methicillin-resistant *S. aureus* [158]. The developed system proved to have the potential to combat implant infections related to osteomyelitis. Moreover, the findings demonstrated better stem cell proliferation; osteogenesis and cell differentiation on the surface of HACC-loaded bone cement compared to antibiotic gentamycin-loaded bone cement [159]. Therefore, quaternized chitosan-based derivatives HACC finds biomedical roles in osteogenic activity, arthroplasty, and gene expression osteogenesis [160].

Furthermore, HACC with 6%, 18% and 44% degrees of quaternization coated on the titanium surface have been utilized for the evaluation of biofilm preventing efficiency. Titanium-based bioactive agents are widely used orthopedic implants due to their biocompatibility, mechanical strength, corrosion resistance and light weight. However, these implants provide a favorable environment for bacterial colonization followed by biofilm formation. Thus, prolonged application was compromised with defective osteoproliferation, poor osteogenesis and serious microbial infections. HACC-coated titanium implants would overcome the above issues with an enhanced anti-infective effect at the same time. HACCs (18% and 44% degree of quaternization) were biocompatible with osteogenic cells and significantly eradicated the developed biofilm around orthopaedic implants at very low MIC values [161].

Yang et al. (2016) extended biomedical applications of HACC-modified titania nanotubes to improve the in vivo anti-infection potential. Orthopaedic intramedullary nails are widely used for the treatment of open and closed 'tibial and femoral' fractures. However, there may be postoperative infections due to implanted intramedullary nails [162]. A high dose of antibiotics is recommended that causes systemic toxicity and osteomyelitis, and delays bone cells proliferation. Hence, implants with an advanced anti-infective property are required to fix the high rate of infections. This innovative research detailed formation of various titania nanotube (NT) loaded with HACC (NT-H) and chitosan (NT-C) and evaluated their comparative cytocompatibility, antimicrobial efficiency and osteoblastic activity against human bone marrow mesenchymal stem cells. The developed NT-H depicted impressive osteogenic action compared to other NT and NT-C nanotubes when assessed on a rat model having femoral medullary cavity implantation and methicillin-resistant *S. aureus* infection. Superior antibacterial effect, cytocompatibility, and profound osteogenesis focused the clinical application of NT-H to manage orthopedic surgical implant-related infections.

Kadama et al. (2021) studied the antibacterial effect of HACC-coated 3D-printed titanium cage during the treatment of improper intervertebral disc space in a rat model. Ti-HACC and non-coated Ti with bioluminescent *S. aureus* were inserted in the caudal discs of model rat. From the in vivo imaging system (IVIVS), the post-operative infection-related changes such as bone destruction and the movement of the implanted cage were assessed on the first, third, and fifth day through micro-computer tomography. The outcomes defined the vital role of Ti-HACC for effective wound healing, improved tartrate-resistant acid phosphate-positive osteoclasts, better antibacterial action against *S. aureus* and preservation of structural damage in caudal disc in rat [163].

4.2. Dental Care and Cosmetics

Chitosan derivative N-[(2-hydroxy-3-trimethylammonium) propyl chitosan chloride, HTCC has better solubility in neutral and alkaline solutions. HTCC has been utilized for the preparation of dental care products owing to its enhanced antimicrobial action [164]. Quaternized chitosan and its substituents have promising action in reducing dental plaque associated with various pathogens. *Porphyromonas gingivalis*, *Actinobacillus actinomycetemcomitans*, *Streptococcus mutans* and *Prevotella intermedia* cause plaques and periodontal diseases. Endodontic cements based on QCh derivatives reduce inflammation and facilitate bone regeneration [165]. Literature reports promising antibacterial action of HTCC against *Enterococcus faecalis* that is associated with endodontic infection. *E. faecalis,* a Gram-positive bacteria, has been isolated from persistent endodontic infection that may cause severe root canal disorder. This pathogen may exist in non-culturable conditions and maintain viability through the year without requiring nutrients, thus damaging dentinal tubules and develop biofilms. Once biofilm is formed, *E. faecalis* becomes more virulent, can protect itself either from adverse condition or high doses of antibiotics [166].

Patel et al. (2020) explored the antibacterial efficiency of chitosan and HTCC against *E. faecalis* pathogen in the state of planktonic and biofilm. A colony-forming-unit study was performed to define the status of three strains of *E. faecalis* (ATCC 29212, P25RC, P52Sa) after treating with serially diluted (20–2500 µg/mL) chitosan and HTCC. Both chitosan (70 µg/mL) and HTCC (140 µg/mL) exhibited significantly higher antibacterial efficacy in double-distilled water as compared to phosphate-buffered saline. The presence of charged ions (Na^+, K^+, Cl^- and $H_2PO_4^-$) in phosphate-buffered saline might disrupt the involved electrostatic interaction that results in less antibacterial action [167]. Moreover, the biocompatibility of natural biopolymer chitosan and its derivative HTCC for the purpose of sealing/obturation of the root canal is far better, compared to other traditionally employed toxicity elicited substances such as zinc oxide, glass ionomers, resins, calcium hydroxide, etc. [168].

Thus, the biocompatibility and characteristic antibacterial efficacy of both chitosan and HTCC focus biomedical application in root canal therapy [169]. Lee et al. (2018) examined the antifungal activity of quaternized chitosan '2-[(acryloyloxy) ethyl] trimethylammonium' as tissue conditioner in the pathological condition 'denture stomatitis'. *Candida albicans* is a main etiological cause for denture stomatitis that affects mucosa underneath diseased teeth. QCh-based tissue conditioner of size 1 mm thickness and 10 cm diam-

eter was prepared and co cultured with *C. albicans*. Significantly diminished fungal colonies were observed with less than 5% QCh concentration compared to the resin denture base. Moreover, this amount did not affect the viability of gingival epithelium cells [170]. Table 6 collects novel research reports on QCh-based systems that have been explored for dental and cosmetic applications.

Table 6

Research highlights few dental/cosmetic uses of QCh derivatives.

QCh-Based System	Biomedical Application	References
Conjugates of chitosan and HTCC	Antibacterial activity against oral pathogen	[172]
Thermosensitive CS-HTCC/GP-Chlorhexidine hydrogel	Local drug delivery for periodontal treatment	[135]
CS-HTCC/GP thermosensitive hydrogel	Antibacterial efficient activator for periodontal pathogens such as *Porphyromonas gingivalis*, *Actinobacillus actinomycetemcomitans* and *Prevotella intermedia*.	[173]
Conjugate of Quaternized carboxymethyl chitosan (QCMC) and calcium hydroxide	QCMC strongly induced reparative dentine formation and showed a better ability in dentin inducing compared with calcium hydroxide.	[162]

Quaternized chitosan derivatives are highly utilized for the preparation of cosmetics including skin creams, shampoo, sprays, and dental remedies. Being natural with exclusive biological features, these biopolymers find an attractive domain in cosmeceuticals. Water-soluble quaternized chitosan (73% degree of quaternization) has been grafted with cyclodextrin (QCD-g-CS) to improve its antibacterial effect against several microorganisms, namely *C. albicans*, *S. mutans*, and *S. oralis* [171].

Sakulwech et al. (2018) extended the study by uploading the negatively charged hydrophilic guest (hyaluronic acid) on the QCD-g-CS to improve penetration enhancement. Hyaluronic acid is generally applied in skin remedies owing to improved skin elasticity, an anti-wrinkle effect and the retention of moisture content. Furthermore, it is popularly used for treating osteoarthritis and manifesting wound healing. The high molecular weight of hyaluronic acid limits its benefit in cosmetics. Amalgamation of quaternized chitosan and cyclodextrin facilitated enhanced solubility, absorption, and bioavailability to the dermal cells. The developed nanoparticles enhanced the penetration of hyaluronic acid in deeper tissues and provided a moisturizing effect. The developed nanoparticles were safe when investigated against skin fibroblast cells [174].

Khalaji et al. (2020) developed biocompatible and antibacterial scaffolds with a blend of synthetic PVA and natural water-soluble HTCC. Fabricated scaffolds exhibited sufficient mechanical strength that was appropriate for skin regeneration during dermal damage. Moreover, the embedded collagen provided additional biological properties, such as extracellular matrix simulation, better cell attachment and proliferation. Hence, fabricated scaffolds can be medically utilized as skin care products [175]. Chen et al. (2017) developed nanocomposite containing quaternized carboxylated chitosan and organic montmorillonite through solution-induced intercalation. A cosmetic cream against skin aging was prepared that exhibited better moisture adsorption, efficient UV protection and moisture retention behaviour without dermal irritation owing to the presence of quaternized carboxylated chitosan [22].

5. Future Prospective

Quaternized chitosan (QCH) derivatives have been extensively utilized for biomedical applications (tissue engineering, drug/gene delivery, antimicrobial, antiviral and immunoadjuvant) owing to their bio and cytocompatibility attributes. With the advancement of nanotechnology, QCH together with nanocomposites (carbon nanotubes and nanofillers) provide superior alternatives to the new arena of drug delivery and regenerative medicines. The reports and findings detailed that QCH derivatives are increasingly focused for the formulation of vaccine adjuvants, chemotherapeutic agents, ecofriendly textiles, and purified membrane matrix. Improved physicochemical properties including improved solubility, mucoadhesiveness, absorption and bioavailability pave QCH derivatives for the synthesis of less invasive and more effective formulations for the management of diverse disorders.

6. Conclusions

Multifunctional QCh derivatives have attracted high attention in the last two decades by their inherent virtues that have broadened biomedical applications. Reports cite extensive research on QCh-based drug carriers, vaccine adjuvant, anticancerous nanoparticles, antibacterial hydrogel, tissue scaffolds, and purification membranes that explore their exclusive physiochemical and biological actions. Furthermore, QCh derivative polymers exhibit high stability, biodegradability and biocompatibility that are essential benchmark for successful therapeutic remedies. However, the synthesis of QCh derivatives including pyridinium and phosphonium salts should be properly channelized at an industrial level to expose their superior biomedical applications on a large scale.

Author Contributions

Conceptualization, K.P., S.K.M., T.B. and A.N.; investigation, A.S. and S.S.; resources, R.G.; data curation, S.S.; writing—original draft preparation, K.P., S.S., A.S. and T.B.; writing—review and editing, A.N., S.B. and T.B.; visualization, S.S.; supervision, A.N. All authors have read and agreed to the published version of the manuscript, and have equal contribution to this paper.

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REVIEW ARTICLE

1,3,4-oxadiazole and its derivatives: A review on recent progress in anticancer activities

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Abstract

The 1,3,4-oxadiazole nucleus is a biologically imperative scaffold possesses numerous biological activities. The broad and potent activity of 1,3,4-oxadiazole and their derivatives has established them as important pharmacological scaffolds especially in the treatment of cancer disease. Several di-, tri-, aromatic, and heterocyclic substituted 1,3,4-oxadiazole derivatives have been reported to possess potent anticancer activity. These substituted 1,3,4-oxadiazoles had shown different mechanism of action and participated in anticancer drug discovery and development. This review is complementary to earlier reviews and aims to review the work reported on anticancer activities of 1,3,4-oxadiazole derivatives from year 2000 to the beginning of 2020.

CONFLICT OF INTERESTS

There is no conflict of interest.

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Review article

PSYCHOLOGICAL DISTRESS IN HEALTHCARE WORKERS DURING COVID-19 PANDEMIC

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ABSTRACT

With the sudden outbreak of coronavirus disease of 2019 (COVID-19) pandemic, the Health Care Workers (HCWs) have claimed varying echelons of stress, anxiety and insomnia. This is the first write up ever reported describing the numerous studies conducted globally to determine the mental health issues in HCWs throughout in COVID-19 pandemic. Herein we compile the studies conducted in different countries worldwide. All these studies alleged high pervasiveness of stress, anxiety, depression, insomnia, somatization, obsessive-compulsive symptoms and other mental disorders in HCWs. Female medical staff showed high occurrence of mental distress over male medical staff. Transmission of infection from HCWs to their family members further increases fear and distress. Ample education, training, psychosocial services and social support have improve mental health of HCWs.

Keywords: Anxiety, Stress, Depression, Mental Health, Psychology, COVID-19

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INTRODUCTIION

Human disease is an impairment of the usual state of a human being that disturbs or modifies its vital functions. Numerous drugs and technologies have been reported till date for the betterment of humanity. Recently, researchers focusing on new technologies including nanotechnology and drug design techniques for the treatment of these diseases.[1-4]

In December 2019, the sudden outbreak of a 2019 novel coronavirus (2019-nCoV) originated from Wuhan, China, threatens the world that has rapidly spread globally and has now been declared as a pandemic by the WHO. 2019-nCoV is the causative virion of coronavirus disease of 2019 (COVID-19) pandemic, having spherical or pleomorphic enveloped, positive-sense, single-stranded RNA (possibly largest known genome of size between 26 kb and 32 kb) having nucleoprotein. Recently, COVID-19 pandemic has become a clinical threat not only to general population but also to healthcare workers (HCWs) worldwide and entire scientist, researchers and physicians all over the countries focused to find the treatment of this pandemic disease.[5]

Mild to severe symptoms of COVID-19 appear from 2 - 14 days after exposure. Fever, cough and tiredness are the common signs and symptoms, while muscle aches, chills, headache, chest pain, shortness or difficulty in breathing, sore throat and smell or taste loss are the other symptoms. Other less common symptoms, including nausea, vomiting and diarrhea have also been reported. Although favipiravir in combination with hydroxychloroquine and corticosteroids and many other drugs had recommended against 2019-nCoV, but still they are not the guarantee treatment of COVID-19.[6]
The ruined spread of 2019-nCoV over international travel density and immune naivety of the population, triggering urgent, draconian public health measures in many countries. The problem is more decisive for HCWs who are serving in COVID care centers. Psychological distress and mental health illness are the adjuvant symptoms of COVID-19 pandemic. As the

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number of patients and occupancy of COVID-19 increases, the mental distresses also increases and urge the psychiatric treatment require not only for infected but also for health care professionals.[7] The enduring mental health impact of COVID- 19 among the common population, children, elderly, wandering workers and healthcare professionals increases the demand of mental health care from specialist professionals. However, to date, there is no specific recommendations issue for both general populations and HCWs from any international agencies mentioning the mental health issues during this COVID-19 pandemic. The fear for COVID-19 among the public appeared more as compared to the severe acute respiratory syndrome (SARS) outbreak, possibly due to increased air mobile and engrained global connectedness made the extent of COVID-19 appeared much more rambling. Furthermore, all-embracing coverage of corpus media, influences the psychological retort of the community to the COVID-19 threat, and further aggravates anxiety among community even when it is used to hearten them to take precautionary and preventive measures to guard themselves from the virus.[8]

Psychological Distress in Pandemic Condition

At the time of the SARS outbreak, 18% - 57% of HCWs claimed emotional distress. Similarly, during Ebola outbreak numbers of medical practitioners including HCWs were experienced psychological disturbance due to over workload and settings without any protective tools and ambitious mainly by empathy. Alike to SARS and Ebola, COVID-19 pandemic state is not so differ, and poses a more significant mental health effect on the medical practitioners.[9]

Although it is difficult to predict mental health consequences of the COVID-19 impact, however elevating rates of anxiety, depression, posttraumatic stress disorder (PTSD) and negative societal behaviors have been reported in health care workers. Healthcare workers remain worried for their relatives to be infected by their own transmission and thus avoid coming in contact with their family members.

A study was designed and conducted to assess the psychological impact of COVID- 19 on HCWs and to compare it to that of stress brought on by Middle East respiratory syndrome coronavirus (MERS-CoV) epidemic in Saudi Arabia.[10] 811 HCWs was recruited to measure mental distress during COVID-19 pandemic, along with Generalized Anxiety Disorder (GAD-7). About 71.8% (582 out of 811) HCWs completed the survey questionnaire, in which about 40% were bared before to MERS-CoV infection. HCWs were reported more anxious about transmitting COVID-19 to a family member rather than acquiring the infection themselves and 41.0% staff was more stressed about COVID-19 as compared to MERS-CoV, while stress level was found to be equal in both infectious diseases. 68.25% (397) enrolled HCWs claimed for mild anxiety, followed with 20.8% (121) moderate anxiety, 8.1% (47) showed high moderate and only 2.9% (17) had very high anxiety against COVID-19 pandemic.

Factors Responsible For Psychological Distress

Demographics and negative society behavior

While taking all protective measures, people remain in fear with the realism of the current and vagueness of the future. Young teenagers and adults are facing uncertainty with respect to their career, professional life and jobs. Fear of infection is creating a panic situation among them. Maintaining a balance between mental and physical health is of utmost prominence to function with optimal clarity.[11] Moreover a negative society's behavior worsens the mental distress reactions (anger, insomnia, uncertainty and fear of illness), health risk behaviors (augmented consumption of tobacco, alcohol and social isolation), mental health disorders (i.e. anxiety disorders, depression, somatization and post-traumatic stress disorder), and lowered perceived health. Mental health professionals must ensure to provide necessary support to both who infected and to those who deliver care.

In India, the first suicidal case was revealed on 12th Feb 2020 in Andhra Pradesh. Although the patient was not infected with COVID-19, still he was so disturbed that in order to protect his family, he quarantined himself and later due to anxiety and fear committed to suicide by hanging himself from a tree.[12]

Increased loneliness and social isolation of HCWs in this pandemic situation, increases psychological distress. Monitoring loneliness and endorsing belongings are candidate mechanisms to protect against psychological distress.[13]

The interference of schedule clinical practice, the sense of loss of control and consequently fear of the impending decline of health services, has annoyed 'overflowing' anxiety and depression among HCWs, a feature which is common of epidemics.[14] Depression is related with deprived medication adherence, which may upsurge morbidity amid older healthcare professionals

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with contemporaneous medical conditions. Seize of freedom of movement with family and friends, steady engagement in leisure deeds and gaining of sustenance and essential items also worsen the psychological poise of HCWs.

Furthermore, as the HCWs had been quarantined, showed severe symptoms of post-traumatic stress as compared to common public who had been quarantined. HCWS also felt more stigmatization than the common public, exhibited additional avoidance behaviors after quarantine, stated more financial loss in terms of income, and were steadily extra affected psychologically: they claimed extensively more annoyance, sadness, worry, fear, frustration, helplessness, loneliness, nervousness, isolation and were fewer happy.

A recent study conducted by Kazmi et al., (2020), to examine the impact of COVID-19 and lockdown on the mental health of the different age groups population of India.[15] Anxiety, depression and stress were investigated among 1000 individuals of different age groups, genders and employment. Young group (15-35 years) showed an increase incidence of depression, while anxiety and stress were prevalent among 21-25 years of individuals. A significant difference for depression and stress level were reported among employed and unemployed individuals, while no significant difference in anxiety level were claimed in both groups.

Chan and Chan (2004) reported that HCWs who were single, had a more jeopardy of emerging adverse psychiatric symptoms as compared to those who were married.[16] The problem is decisive when these HCWs have been quarantined regularly.

Shortage of healthcare workers

As the COVID-19 cases increase rapidly worldwide, the global public healthcare and mental health care emergency prerequisite also amplify. The scarcity of manpower worldwide is the major hurdle to deal with COVID-19 and thus healthcare workers faced an increased workload thru the fright of being infected. These medical responders face heightened stress and become emotionally exaggerated and traumatized. Increased workload, loneliness and segregation further more increase fear, anxiety, and depression and sleep disorders.

The condition is terrifying in those countries having inadequate numbers of mental health professionals in comparison to the forthcoming growth of demand. The most recently data published by Kirton (2020) illustrated that the European countries (Eurostat) including Switzerland having 51.7; in Germany 27.4, in France 22.9, in Italy 17.4, in Croatia 16.1, in Spain 10.5, in Poland 9.2 and in Bulgaria 7.8 numbers of psychiatrists available per 100.000 inhabitants.[17] Even in the U.S., the condition is also alarming and only 11 psychiatrists available per 100.000, while in China it is only 2.2. Furthermore, Marr (2019) reported that in the U.S. 40% lives in scarcity of mental health professionals and even 60% of the population survive without a psychiatrist. Although the availability of adequate numbers of mental health professionals and psychiatrists are not the warranty that the HCWs will not face the psychological distress and mental illness in times of the ongoing pandemic.

Poor working conditions

Health professionals working in critical care units like ICU, especially, require mental health professionals to reduce stress levels and risk of depression. These HCWs remains in fear of high chances of exposure risk possibly due to highly contagious with multiple transmission route, high exposure dose, long daily contact hours, and ICU stay.

Recently, Naushad et al., (2019) reported that the HCWs who works in emergency departments and or intensive care units had a high risk of mounting psychiatric outcomes than those working in other departments.[18] Working in isolation wards or containment zones further increase anxiety and fear of becoming infected.

According to World Health Organization (WHO) guidelines COVID-19 can be transmitted chiefly from person to person from nose or mouth in the forms of droplets. Thus aerosol generating procedures, including all trans oral interventions, nasal endoscopy, laryngoscopy and tracheostomy deemed to put medical professional at high risk of viral infection and thus International Head and Neck Scientific Group (IHNSG) advised to avoid all these aerosol generating procedures and recommended only to use in emergency.

Psychological Distress Among Healthcare Workers

Kang et al., (2020) reported first the mental health of 994-medical and nursing staff in Wuhan, China.[19] Of all participants, mental health disturbances were reported sub threshold (36.9%), mild (34.4%), moderate (22.4%) and severe (6.2%) in the instant rouse of the viral epidemic. Young women were heavily disturbed. Importantly, managing tactics were varied in all applicants ranging from perusing psychological materials (36.3%), psychological resources through

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media (50.4%), and contributing in counseling or psychotherapy (17.5%).

Lai et al (2020) investigated the stress of unfamiliar environment among 1257 HCWs in 34 hospitals of China in COVID-19 pandemic.[20] These HCWs were directly engaged in patients care, who were suspected or confirmed COVID-19 positive. 70% of HCWs reported distress, while 50% reported depression of 1257 HCWs. Similarly, Lv et al., (2020) reported overall 34.7% anxiety incidence and 24.8% mild anxiety incidence among 8028 doctors and nurses of 8 provinces (i.e. Beijing, Guangdong, Hainan, Hebei, Henan, Hubei, Jiangxi and Shanxi) of China.[21] The authors concluded that Chinese medical staff suffered from the psychological disorders. Table 1 represents mental health stress of HCWs around the world.

Table 1: Mental health stress of HCWs, reported in different countries.

Country	Number of HCWs	Stress	Anxiety	Depression	Sleep Disturbance
China	1257	70%	-	50%	-
China	8282	-	34.7%	-	-
Italy	1379	49.38%	19.80%	24.73%	8.27%
Jordan	1,006	-	34%,	19%,	29%
Spain	1459	80.6%	-		-
China	1563	73·4%	44·7%	50·7%	36.1%

A pathetic condition has been aroused in Philadelphia on Thursday, 19 March 2020, when health commissioner Dr. Thomas announced 10 of the 44 people with the Covid virus are healthcare workers.[22] This report brought a major depression among HCWs.

Spanish physicians Fernández and coworkers (2020) conducted a national self-reported online questionnaire started on 29 March to 5 April 2020 among 781 HCWs including 385 physicians, 233 nurses, and 164 other professionals and 1006 non-HCWs.[23] Anxiety, depression and acute stress related questions were asked and measured on Hamilton Anxiety Scale (HARS), Beck Depression Inventory (BDI), and the Acute Stress Disorder Inventory (ASDI). For anxiety, no significant differences were observed between HCWs (M 18.2, S.D. 10.4) and non-HCW (M 16.9, S.D. 10.3). While greater depressive symptoms were reported in HCW ($\chi 2 = 2.9$, $p = 0.09$) as compared to non-HCWs. Furthermore, higher symptoms of acute stress were reported in HCWs (M 4.9, S.D. 3.1) than non-HCW (M 4.3, S.D. 3.1). These findings suggested that HCWs have greater impact on mental health than in non-HCWs; even nurses and physician trainees are the most vulnerable groups.

Rossi et al., (2020) reported first in Italy the psychiatric distress among HCWs during COVID-19 pandemic.[24] A web-based study data were collected between 27 March to 31March 2020, using an online questionnaire. HCWs of Italy could only be participating. 1379 HCWs were participated in online questionnaire and responds. 273 (19.80%), HCWs claimed anxiety; 114 (8.27%) insomnia; 341 (24.73%) depression; 681 (49.38%) respondents endorsed PTSS and 302 (21.90%), high perceived stress. Younger age and female sex were associated with all investigated outcomes except insomnia, while General practitioners were more likely to endorse PTSS than other HCWs. Health care assistants and nurses claimed severe insomnia. The author's claims mental health issues in HCWs during COVID-19 pandemic, especially in young women and frontline practitioner. Further monitoring and specific interventions for HCWs were suggested to minimize long-term mental health–related disabilities.

Recently, a very impressive study was conducted and reported by Pappa and colleagues (2020) in Brain, Behavior, and Immunity Journal.[25] A data was obtained available online up to April 17th 2020. The review protocol is registered in PROSPERO and total 33062 participants were enrolled in the study. Anxiety, depression and insomnia were reported among HCWs in COVID-19 pandemic. 29.06% female and 20.92% male HCWs reported for anxiety, while 26.87% female and 20.34% male suffered from depression. The nurses showed higher (25.80%) anxiety as compared to doctors (21.73%); similarly greater depression rate was reported in nurse (29.65%) over doctors (24.5%). These results showed gender and occupational differences. Female HCWs and nurses showed higher rates of affective symptoms compared to male HCWs and medical staff respectively.

Benjamin et al., (2020) investigated the psychological distress of HCWs in Singapore in the midst from 19 February to 13 March 2020.[26] All HCWs showed the incidence of anxiety, depression, stress, and PTSD. The nonmedical HCWs were reported at highest risk for psychological distress as compared to medical HCWs during this COVID-19 outbreak.

Alike of mental health issue in HCWs worldwide, in UK HCWs also reported unprecedented mental pressures during the dealing with the COVID-19 pandemic. Choudhury et al., (2020) reported the psychological distress amongst 106 healthcare workers, who were

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working in a cardiac centre in the North West of England in this COVID-19 pandemic outbreak.[27] During the time, the centre was anticipating the arrival of large numbers of Covid-19 patients and the hospital had started receiving some earlier cases. Mild anxiety was reported in 27%, moderate in 12% and severe in 22% of survey participants. Women reported higher anxiety levels as compared to men. However, no significant differences in anxiety were reported on the basis of occupation, direct exposure to patients, age or length of NHS experience.

An Ireland physician Gavin and his team members (2020) reported 25% of HCWs were positive for COVID-19 sin Ireland, which was higher than Italy and Spain.[28] Higher positive cases in HCWs amplified fears of healthcare workers that may become ill and unable to care for or risk infecting their children. The authors reported psychological impact on Covid-19 frontline healthcare workers, high rates of anxiety, depression, distress and insomnia.

Tsamakis and colleagues (2020) reported the psychological burden on healthcare professionals in Greece during COVID-19 pandemic. Authors discussed potential measures to minimise psychological distress among frontline HCWs against this biothreat.[29]

An online survey among 1,006 practitioners (55.3% females) was conducted during a stringent lockdown in Jordan. Exhaustion (34%), anxiety (34%), depression (19%) and sleep disturbances (29%) were reported.[30] Salgado et al., (2020) described psychological distress level and Sense of Coherence (SOC) of healthcare professionals of Spain during COVID-19 crisis. 80.6% of healthcare professionals had shown psychological distress with mean score on the SOC-13 scale was 62.8 points (SD = 12.02).[31]

Recently, Zhang et al., (2020) reported the survey outcomes in Frontiers in Psychiatry. The survey involved 1563 medical staff, reported that 50·7% of medical staff found the incidence of depression, 44·7% had anxiety and 36.1% sleep disturbance. 73·4% of medical staff showed stress related symptoms. These outcomes may guide health authorities to allocate health resources and to generate suitable treatments for medical staff who have mental health problems.[32]

Very recent psychological intervention study was conducted by Huang et al., (2020) among 230 healthcare professionals who were involved in the treatment of COVID-19 in China.[33] The Self-rating Anxiety Scale (SAS) and PTSD- Self-rating Scale (PTSD-SS) were generated. 53 out of 230 (23.04%), healthcare professionals reported incidence of anxiety, while the severe anxiety (2.17% i.e. 5/230), moderate anxiety (4.78% i.e. 11/230) and mild anxiety (16.09% i.e. 37/230). Female medical staff showed higher incidence of anxiety as compared to male medical staff [25.67% (48/187) vs 11.63% (5/43) respectively], while nurses showed higher anxiety as compared to doctors [26.88% (43/160) vs 14.29% (10/70)]. These results showed high occurrence of anxiety and stress disorder among medical staff and suggested the psychological skills training of medical staff. Female nurses require more attention for mental health treatment.

Furthermore, an online survey was conducted from 19 February to 06 March 2020 by Zhang and colleagues in China, over 2,182 HCWs including both nonmedical health workers (no. 1255) and medical health workers (no. 927).[34] Medical-HCWs showed high prevalence of insomnia (38.4%), anxiety (13.0%), depression (12.2%), somatization (1.6%) and obsessive-compulsive symptoms (5.3%) over nonmedical-HCWs (30.5%; 8.5%; 9.5%; 0.4% and 2.2%) respectively. Medical HCWs had organic disease was an independent factor for anxiety, depression, insomnia, somatization and obsessive-compulsive symptoms; while nonmedical HCWs had organic disease was at risk factor for depression, insomnia and obsessive-compulsive symptoms. Female HCWs, lived in rural area were reported to be at vulnerable risk factors for anxiety, depression, insomnia and obsessive-compulsive symptoms.

Wang and co-authors (2020) investigated the instant psychological responses and associated factors during the early stage of COVID-19 outbreak in Mainland China among the common population.[35] Results showed that 53.8% of respondents claimed moderate or severe psychological impact, while 28.8% and 16.5% reported moderate to severe anxiety and depressive symptoms respectively.

Coping Strategies for Psychological Distress

After the first outbreak of COVID-19 in Wuhan, Hubei province, China, the indigenous government of Wuhan had executed the policies, addressing the mental health problems in infected medical staff. Almost 1230 medical HCWs had been called from different provinces to Wuhan for patients care, strengthen logistics support, and to lessen the work pressure on medical workers. A

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shift system has been introduced to provide rest for front-line medical workers and to reduce work pressure. Online platforms had been generated to minimize the risk of transmission between the patients and medical staff. In Ren Min Hospital of Wuhan University and Mental Health Center of Wuhan, a psychological intervention team had been set up to provide mental support for HCWs. Hundreds of HCWs received these interventions, and reported worthy response, and their provision is mounting to extra persons and hospitals.

Chen et al., (2020) vividly illustrated a detailed psychological intervention plan of The Second Xiangya Hospital China for their HCWs, to maintain their mental health.[36] The plan covered three areas including a development of psychological intervention team to provide online materials; a psychological assistance hotline team to guide, supervise and to solve psychological problems; and psychological interventions for group activities. However, healthcare workers showed reluctant to participate in this programme and programme was redesigned and included rest area, guaranteed food, and record video sharing facilities with their families. The rest area was periodically visited by a counsellor. More than 100 HCWs could rest at a time, and most of them report feeling at home in this accommodation. A remarkable result were obtained among HCWs and recommended to include ongoing feedback and modification of such programmes.

Currently, in Ontario, within a week, more than 450 licensed social workers, psychologists and psychotherapists registered themselves to provide free telephone therapy sessions to HCWs in COVID-19 pandemic. While in Canada, medical students offer their services (e.g., household tasks, conveying groceries and providing child care) to HCWs in need.[37] All these tack ticks can lessen the effect of quarantine or isolation and aid to preserve wellness, and fitness in HCWs so that they can return to work when able.

Blake and coworkers, (2020) utilized Agile methodology for the development and evaluation of a digital learning package for the wellbeing for all UK HCWs.[38] The package had been accessed 17,633 times within 7 days and HCWs claimed higher satisfaction with it's content, usability and utility. The most important feature of this e-package was free of cost, and direct provides digital support on 'psychological wellbeing for healthcare workers'.

Timely monitoring and reporting mental distress reactions and mental health disorders in general populations and vulnerable groups, including front-line workers, should be the priority to minimize the self-harm and suicide attempts.

Guidelines to Reduce Psychological Burden of COVID-19

According to WHO, it is paradox that still there is no adequate guidelines previously available for HCWs who have been dealing with exposed individuals to provide counseling and psychiatric screening facilities to fight against anxiety, depression and suicide temper. WHO reports of 2020, further claims that numerous physicians develop anxiety, depression, PTSD and burnout after the cessation of the pandemic.

On 18 March 2020, WHO released the guideline regarding the psychosocial deliberations during this COVID-19 outbreak for the general population, healthcare workers, for team leaders or managers, for children to their carrier, for old age people and for people in isolation.

Considering the mental health response in medical staff, National Health Commission of China issued a guideline of psychological emergency intervention for 2019-nCoV on dated January 27, 2020. It was the first guideline in China, exploring the multifaceted psychological fortification of the mental health of medical workers.

CONCLUSION

Healthcare workers remain at increased peril of moral harm and mental health problems and need to proactive steps to protect their mental wellbeing during this COVID-19 pandemic. HCWs must be vigorously monitored, supported, and, where necessary, provided with evidence based treatment. Reducing stress by capitalizing on coping policies akin to encouraging lifestyle behaviors can enormously improve mental health well-being. Continuing convention with loved ones either direct or through social media with maintaining precautions also helps to reduce fear and anxiety. Engaging in habitual physical work, eating healthy food, practicing good sleep hygiene where possible, and guaranteeing sufficient rest and breaks between shifts have been recommended by the WHO. Avoid tobacco and consumption of alcohol or other drugs also beneficial for mental health.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Discovery of Novel 1,2,4-Oxadiazole Derivatives as Potent Caspase-3 Activator for Cancer Treatment

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Abstract

In the present study, a quantitative structure–activity relationship (QSAR) and docking studies were accomplished on a series of 1,2,4-oxadiazoles. The results of QSARs are reliable and have high predictive ability for both the internal (q^2 = 0.610) and external (pred_r^2 = 0.553) datasets with least standard error (SE; i.e., 0.130) and four principal components, which signifies the reliability of the generated model. Molecular docking was also reported by the GOLD docking program, which showed that the hydrogen bonding may be responsible for the activity, and may be further increased upon adding high electronegative substitutions.

Keywords: 1,2,4-oxadiazole (/search?q=1%2C2%2C4-oxadiazole); **apoptosis (/search?q=apoptosis)**; **caspase (/search?q=caspase)**; **docking (/search?q=docking)**; **QSAR (/search?q=QSAR)**

1. Introduction

Cancer is the second leading cause of mortality globally and becomes the principal cause of mortality in developing countries [**1**,**2**,**3**]. Recently, several anticancer drugs have become available on the market, acting through different mechanisms; however, the majority of them are associated with serious side effects [**4**,**5**]. The lack of targeting ability of these drugs is responsible for their side effects [**6**]. Large numbers of heterocyclic compounds have been reported for potential anticancer activities [**7**]. These heterocyclic-based anticancer agents are either under investigation or marketed as potent anticancer agents [**8**,**9**,**10**,**11**]. Oxadiazole is an important five-membered heterocyclic compound, having one oxygen atom and two nitrogen atoms. Recently, several 1,2,4-oxadiazole derivatives have been shown to possess anticancer activity [**12**,**13**].

Nowadays, researchers are focusing on various groups of molecules that are involved in the apoptosis inducing cytotoxicity. Caspases, a group of cysteine proteases, are the executioners of apoptosis. These caspases cleave their substrates after aspartic acid residues. Initiator caspases (caspase 2/8/9/10) and effector caspases (caspase 3/6/7) are the two classes of caspase. Recently, the activation of caspase-3 mediated apoptosis becomes an interesting therapeutic strategy for cancer therapy. Zhang et al. reported a series of 3-Aryl-5-aryl-1,2,4-oxadiazoles as a novel apoptosis inducer through caspase-3 activation. The compounds' activities have been reported against breast and colorectal cancer cell lines [**14**].

The quantitative structure–activity relationship (QSARs) is an attempt to correlate the structural features of the compounds quantitatively with their biological activities. Researchers reported thousands of QSAR studies in the search for novel anticancer agents [**15**,**16**,**17**,**18**,**19**].

In the search for new anticancer agents, our research group previously reported QSAR studies of 1,2,4-oxadiazole derivatives describing the key structure features responsible for anticancer activities [**20**,**21**,**22**]. In the continuation of our previous work, herein we report the two-dimensional QSAR (2D-QSAR) and molecular docking studies' outcomes.

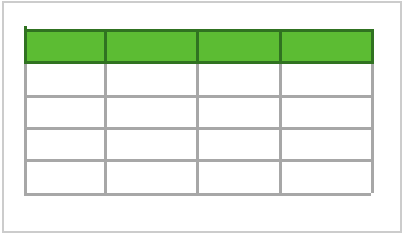
The 2D-QSAR studies were done using Step Wise k Nearest Neighbor Molecular Field Analysis [(SW) kNN MFA] using V-Life Molecular Design Software Version 3.0 (V-Life Molecular Design). The docking studies were also performed using GOLD software.

2. Material and Methods

2.1. Dataset

A dataset of twenty eight 3-aryl-5-aryl-1,2,4-oxadiazoles derivatives has been taken for present QSAR study (**Table 1**). Compounds have high structural diversity with ample range of biological activity [**14**,**23**].

Table 1. 1,2,4-Oxadiazole analogues and their experimental caspase-3 activator activity.



2.2. 2D QSAR

2D QSAR studies were performed via Step Wise k Nearest Neighbor Molecular Field Analysis [(SW) kNN MFA] method using V-Life Molecular Design Software Version 3.0 (V-Life Molecular Design) [**24**,**25**,**26**].

The 2D QSAR studies were performed by dividing compounds in the training and test dataset which resulted several QSAR equations. Unicolumn statistics was done to divide training and test data compounds. Twenty-two compounds were positioned in the training set and 6 compounds (**4b**, **4d**, **4e**, **10a**, **10d** and **11h**) in the test set.

2.3. Molecular Docking Analysis

Molecular docking was employed to locate the appropriate binding orientations and conformations of these 1,2,4-oxadiazoles interacting with caspase-3 using the docking program GOLD version 3.2. Ten docked conformers were produced for each 1,2,4-oxadiazole derivative. The conformation with the lowest docking energy in the most populated cluster is selected as the possible “active” conformation against the 1RE1 active site. In the present study, 28 compounds were successfully docked into the 1RE1 site.

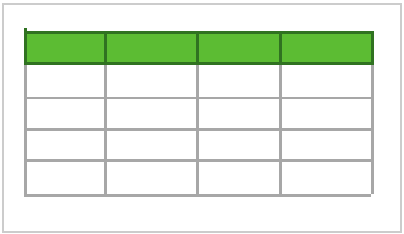
The X-ray crystal structure (pdb: 1RE1) of caspase-3 was obtained from the Protein Data Bank. Initially, for protein preparation, water molecules were removed, hydrogen atoms added and AMBER7FF99 charges to the protein were applied. The ligands were docked inside a cubic GRID box (within 5 A° surrounding to the cocrystallized ligand) centered at the midpoint between the Cys205 and Gly238. Ten docking runs were performed for each compound in the dataset. In most cases the chosen pose was the top ranked solution.

3. Results and Discussion

3.1. 2D QSAR Results

The results of the unicolumn statistics are summarized in **Table 2**, which showed that the test is interpolative i.e., both test and training dataset contain compounds of high structure diversity with variation in biological activity. The test and the training set contained a diverse set of compounds with low, moderate and high biological activity.

Table 2. Unicolumn statistical data of training and test set in 2D quantitative structure–activity relationship (QSAR) models.

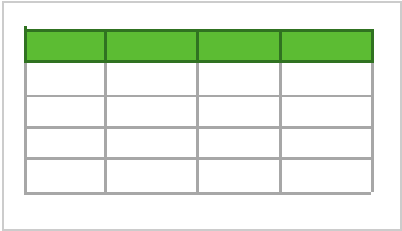


Finally, the following model was selected.

$$pEC_{50} = 0.243 * IP - 0.139 * BC + 0.155 * DM + 0.008 * PSA + 0.0005 \quad (1)$$

The obtained model showed a high correlation coefficient (r = 0.862) between descriptors including ionization potential (IP), bromine count (BC), dipole moment (DM), polar surface area (PSA) and anticancer activities. The squared correlation coefficient (r^2) of 0.743, explains 74.29% of the variance in biological activity. The obtained model is statistical significant with F values F(4,21) = 11.561. The obtained model showed both good internal and external predictive ability with cross-validated squared correlation coefficient for internal dataset (q^2) value 0.610 and for external dataset (pred_r^2) value 0.553 with a standard error (SE) of 0.130 (**Table 3**).

Table 3. Parameters value for the best 2D QSAR model generated.



In the model, the contribution of the descriptors is presented in the contribution chart (**Figure 1**), signifying the positive contribution of the ionization potential (IP), dipole moment (DM) and polar surface area (PSA) towards the biological activity. The addition of substitution that increases the polarity of the compounds results in increased anticancer activity. The negative contribution of the bromine count signifies the lower number of bromine encouraging biological activities.

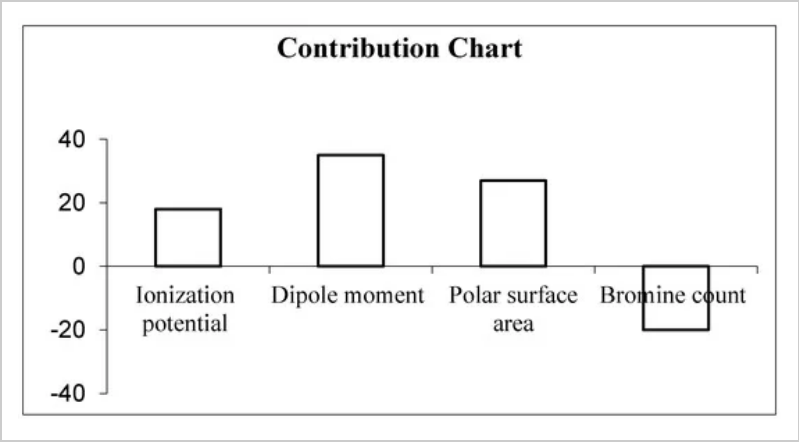


Figure 1. Contribution chart of descriptors in 2D QSAR model.

The correlation between the experimental and predicted activity of the compounds is shown in **Table 4** and represented in **Figure 2**.

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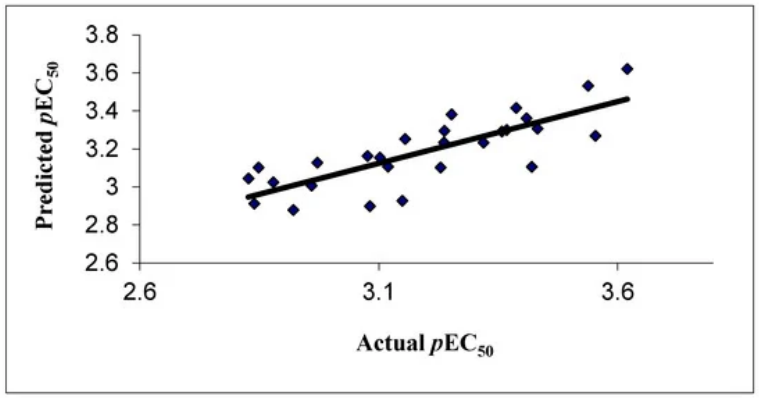

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Figure 2. Correlation of experimental and predicted activity in 2D QSAR model.

Table 4. Experimental, predicted and residual activities of the compounds obtained in 2D QSAR and GOLD score.

3.2. GOLD Docking Studies

All 28, 1,2,4-oxadiazoles derivatives were docked into the binding site of caspase-3 and the energy scores of the activators are also shown in **Table 4**. A precise correlation was observed in between docking scores and pIC_{50} values.

A complete overview of GOLD docking is presented in **Figure 3** and **Figure 4**.

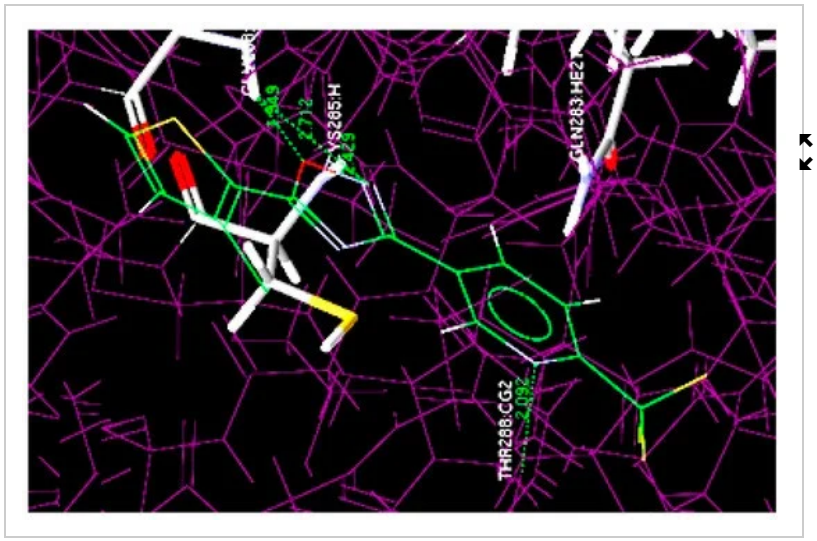

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Figure 3. Overlay of docked highest potent oxadiazole compound (**4m**) at the active site of 1RE1.

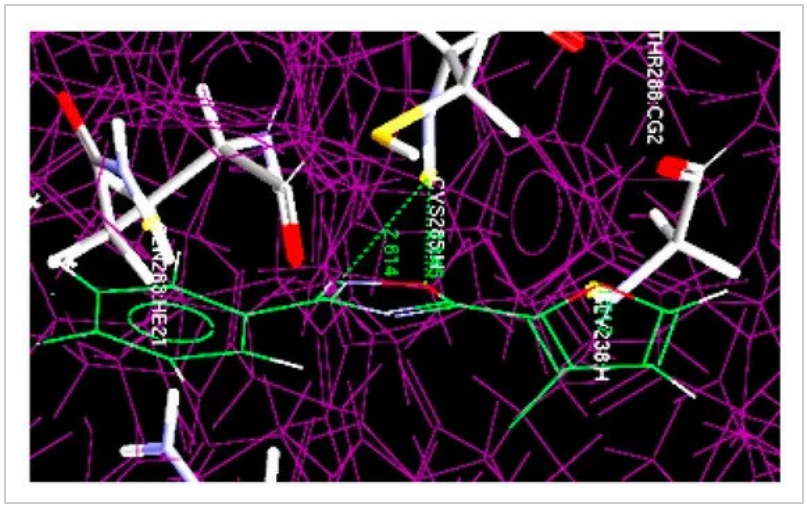

Figure 4. Overlay of docked least potent oxadiazole compound (**10b**) at the active site of 1RE1.

The docking results revealed that most active compound **4m** is properly located at the binding site of the Cys205 and Gly238 amino acid residues and numerous interactions occur between it and the binding region of the enzyme. The four key hydrogen bond interactions occur: (1) between the NH of Gly238 and the O of the oxadiazole ring; (2) between the NH of

Gly238 and the N of the oxadiazole ring; (3) between the NH of Cys285 and the N of the oxadiazole ring; (4) between the NH of THR288 and the N of the pyridine ring residue (**Figure 3**). The hydrogen bonding distances observed were 1.549 Å (O···H-NH-Gly238), 2.712 Å (N···H-NH-Gly238), 2.429 Å (N···H-NH-Cys285) and 2.092 Å between the N of the pyridine ring and NH of THR288 (N···H-NH-THR288).

Akin to compound **4m**, compound **10b** was also docked at the same binding pockets having Cys205 and Gly238 amino acid residues (**Figure 4**). The result showed the formation of two hydrogen bonds: (1) between the NH of Cys205 and the O of the oxadiazole ring (O···H-NH-Cys205), having 2.145 Å bond distance; (2) between the NH of Cys205 and the N of the oxadiazole ring (N···H-NH-Cys205) with 2.614 Å bond length.

The docking results revealed that the hydrogen bonding may be responsible for biological activity, which may be further increase upon adding more electronegative substitutions. The correlation between the dock score and the experimental activity is shown graphically in **Figure 5**, which shows a linear correlation between the dock score and biological activity.

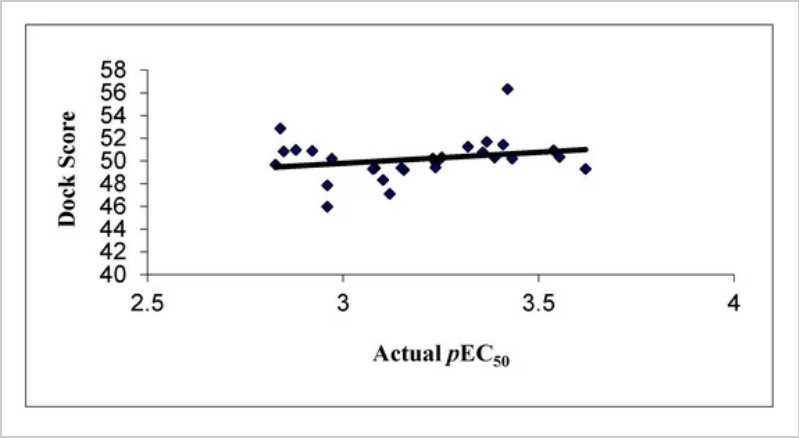

Figure 5. Correlation between the experimental activities and dock score in GOLD docking.

The results of the QSAR analysis clearly show that upon increasing the polarity in terms of theionization potential (IP), dipole moment (DM) and polar surface area (PSA), biological activity will also be enhanced. The docking results also support the QSAR outcomes.

4. Conclusions

In conclusion, the current QSAR studies established a reliable QSAR model with high predictive ability with $q^2 = 0.610$, $r^2 = 0.743$ and low standard error (SE) = 0.130 and four principal components. The predicted value of the external test set (pred_r^2) was also high (i.e., 0.553). The developed model was reliable, which indicated the importance of substitution in 1,2,4-oxadiazoles at their respective positions to improve anticancer activity. The positive contribution of ionization potential (IP), dipole moment (DM) and polar surface area (PSA) is conducive for biological activity, and further addition of these substitutions increases anticancer activity, while the negative contribution of the bromine count signifies the lower number of bromine encouraging the biological activities. The docking results explore the binding mode between the ligands and the receptor.

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Data Availability Statement

Data available in article and raw data are available from the corresponding authors upon request.

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Conflicts of Interest

The authors declare that they have no conflict of interest.

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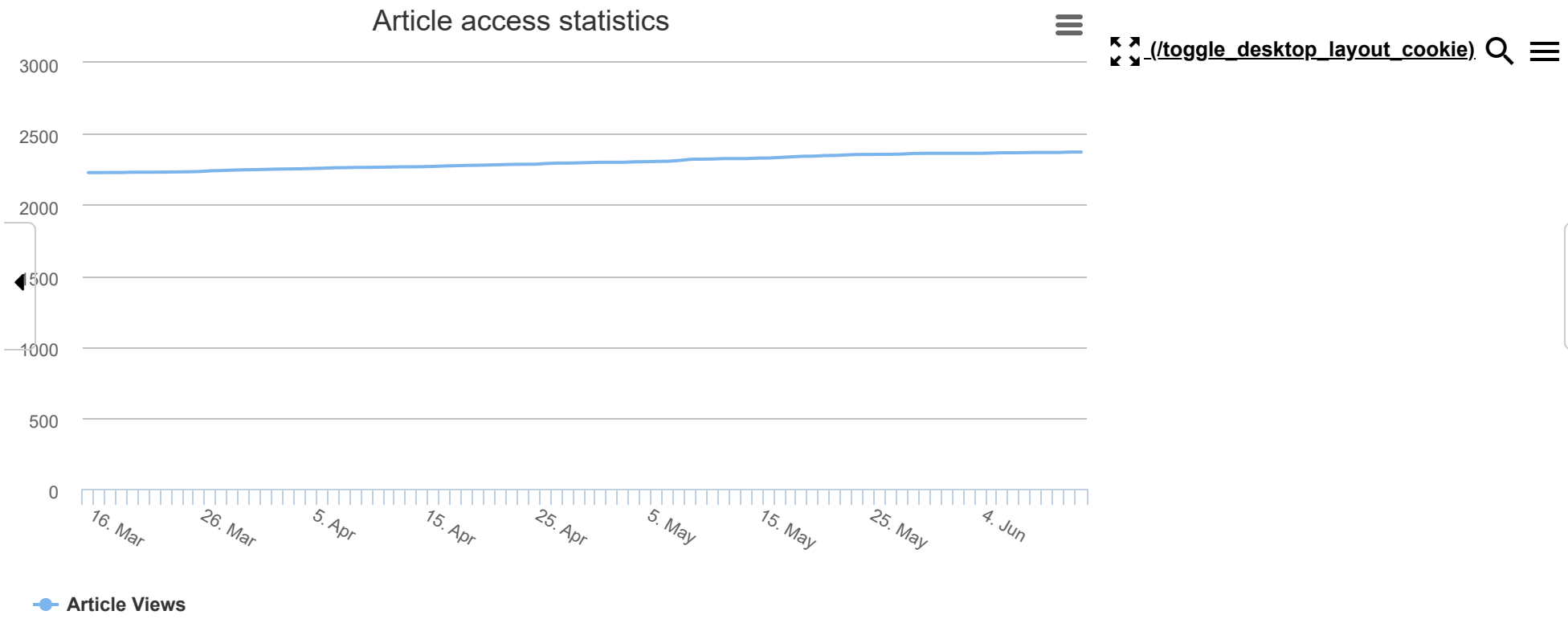

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REVIEW

Caspase-3: A primary target for natural and synthetic compounds for cancer therapy

Poonam Yadav, Ramakant Yadav, Shweta Jain, Ankur Vaidya

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Abstract

Caspases, a group of protease enzymes (cysteine proteases), exist as inactive zymogens in the cells and execute apoptosis (programmed cell death). Caspase-3, an executioner caspase, plays an imperative role in apoptosis and becomes a primary target for cancer treatment. A number of analogues of quinazoline, quinazolinone, indoloquinazolines, quinone, naphthoquinones, pyrroloiminoquinones, styrylquinolines, tetheredtetrahydroquinoline, fluoroquinolone, thiosemicarbazones, benzotriazole, pyrimidines, chalcone, and carbazoles have been reported till date, representing caspase-3 mediated apoptosis for cancer therapy. Simultaneously, plant isolates, including lysicamine, podophyllotoxin, and majoranolide, have also been claimed for caspase-3-mediated apoptosis-induced cytotoxicity. Procaspase-activating compound-1 (PAC-1) is the first FDA approved orphan drug, and its synthetic derivative WF-208 also showed fascinating caspase-3 mediated anticancer activity. Till date, a large number of compounds have been reported and patented for their

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CONFLICT OF INTERESTS

There is no conflict of interest.

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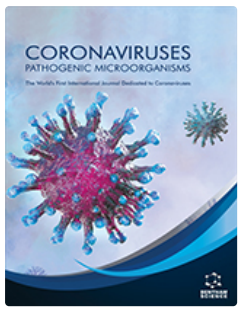

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Research Article

Assessment of Stress, Anxiety, and Depression Levels Among COVID-19 Positive Patients Admitted in Rural Tertiary Care Hospital

Author(s): Ramakant Yadav, Neha Dubey, Shweta Jain, Ankur Vaidya* and Raj Kumar

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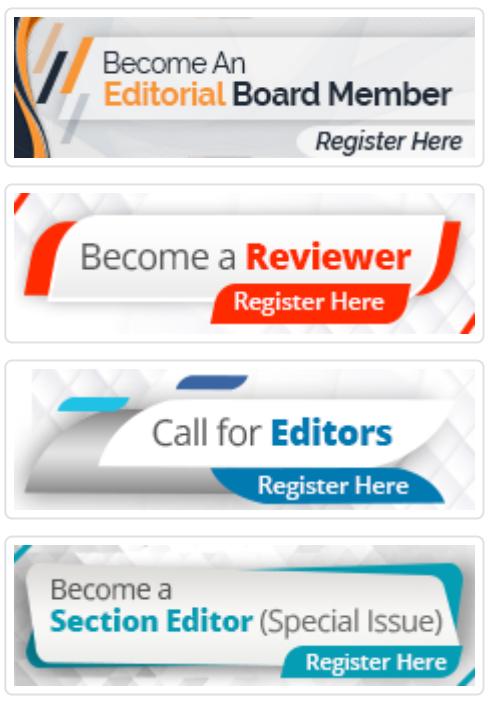

Abstract

Objective: The aim of the present study was to investigate the psychiatric distress, including stress, anxiety, and depression levels, among COVID-19 positive patients who were admitted between 01 July 2020 to 31 August 2020 to the COVID-19 isolation ward of the Uttar Pradesh University of Medical Sciences, Saifai, Etawah India. Participants included 100 patients, with 55 males and 45 females. The majority of admitted patients (81%) were illiterate. Out of 100 patients, 83 were married, 16 were unmarried, and only 1 was a widow.

Methods: Levels of anxiety, depression, and stress level were noted in admitted patients using Generalized Anxiety Disorder-7 (GAD-7), Patient Health Questionnaire (PHQ-9) depression assessment, and Perceived Stress Scale 4 (PSS-4) assessment techniques, respectively.

Results: Patient Health Questionnaire (PHQ-9) depression assessment results showed minimal, mild, and moderate depression in 9, 25, and 66 patients, respectively, with a 10.6 median score of PHQ-9. Mild, moderate, and severe anxiety (GAD-7 score) was present in 22, 28, and 50 of the patients surveyed. The mean Perceived Stress Scale 4 (PSS-4) was also analyzed, and it reported 6.1 values. The results of the study demonstrated that the patients had a high label of psychiatric distress, but still, admitted patients believe that they will come out from this pandemic condition.

Conclusion: Although patients claimed psychiatric distress and mental health illness, they still denied the requirement of any mental health professionals to minimize stress levels and were satisfied with the medical facilities available in a hospital located in a rural area.

Keywords: Coronavirus (COVID-19) , generalized anxiety , depression , perceived stress , psychiatric distress , rural .

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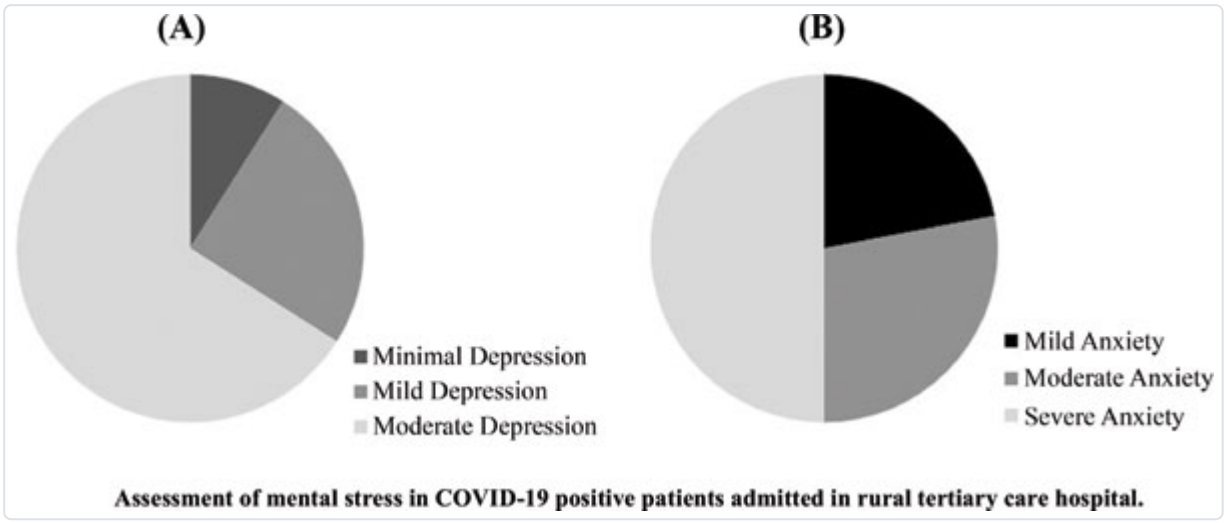

Assessment of mental stress in COVID-19 positive patients admitted in rural tertiary care hospital.

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Some Scaffolds as Anti-leishmanial Agents: A Review

Author(s): Thatikayala Mahender, Wadhwa Pankaj, Singh Pankaj Kumar, Vaidya Ankur and Sahu Sanjeev Kumar*

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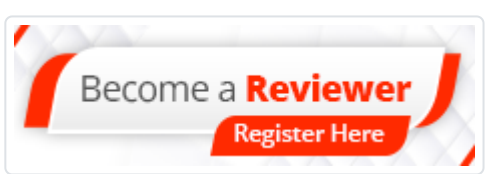

Abstract

Leishmaniasis is a parasitic infectious neglected tropical disease transmitted to humans by the parasites of Leishmania species. Mainly, three types of leishmaniases are usually observed: visceral (VL), cutaneous (CL), and mucocutaneous leishmaniasis. In many western countries, almost 700,000 to 1 million people suffer from leishmaniasis, and it is estimated that around 26000 to 65000 deaths occur from leishmaniasis. Few drugs are available for its treatment; however, none of them are ideal for leishmaniasis due to long treatment, discomfort mode of administration, risk of high-level toxicity, high resistance, etc. Hence, so many patients are unable to take complete treatment due to the high drug resistance. The present

review will focus on antileishmanial activity of reported derivatives of betacarboline, chalcone, azole, quinoline, quinazoline, benzimidazole, benzadiazapine, thiaazoles, semicarbazone, and hydontoin analogues. We believe that this present study will be helpful for researchers to design new antileishmanial agents.

Keywords: Leishmaniasis, antileishmanial compounds, visceral, cutaneous, mucocutaneous, scaffolds.

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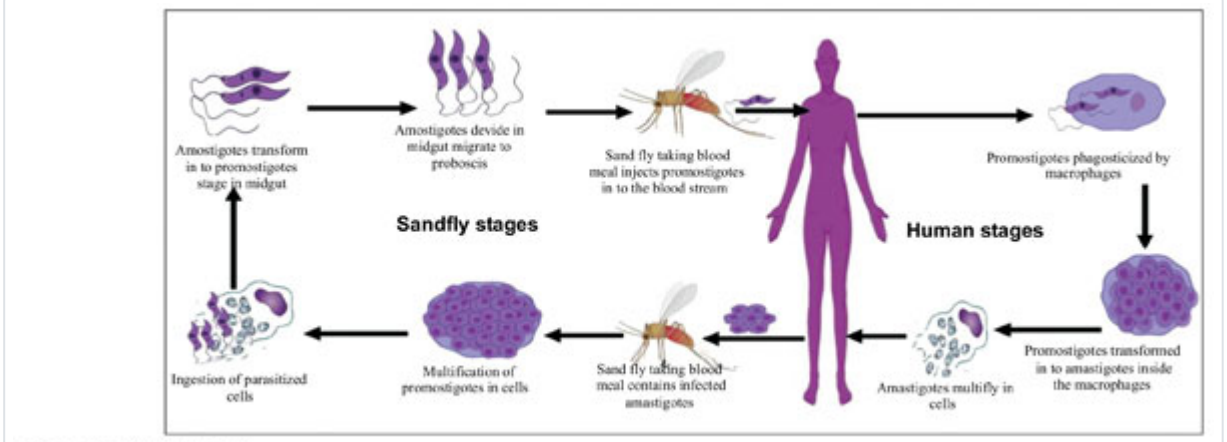

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Open Access Review

Antiarthritic Activities of Herbal Isolates: A Comprehensive Review

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Abstract

Numerous plant species with therapeutic properties, such as antimicrobial, antiinflammatory, antiviral, antimalarial, antiarthritic (AA), antihypertensive, cardiotonic, and so forth, are reported in the literature. Usually, medicinal plants are widely used, and assumed to be safe and cheaper alternatives to chemically synthesized drugs. However, they are not regulated for potency and purity, and thus, care must be taken for their safe use. In this review, we aimed to compile all of the herbal isolates possessing AA properties, including alkaloids (mahanine, 3-acetylaconitine, sanguinarine, jatrorrhizine hydrochloride, and piperine), terpenoids (eugenol, nimbolide, bartogenic acid, cannabidiol, and curcumin), and flavonoids (quercetin, resveratrol, kaempferol, chebulanin, ellagic acid, rosmarinic acid, gallic acid, chlorogenic acid, ferulic acid, and brazilin). These isolates act through numerous pharmacological mechanisms such as inhibiting cytokines, chemokines, or matrix metalloproteinase, etc., to demonstrate AA activity. Animal models utilized for assessing the AA properties of these isolates, including adjuvant-induced arthritis mouse models, are also discussed. Furthermore, nanotechnology-based approaches to deliver these isolates are also reviewed, which have shown improved therapeutic efficacy of isolated compounds.

Keywords: arthritis (/search?q=arthritis); **herbal isolates (/search?q=herbal+isolates)**; **arthritic models (/search?q=arthritic+models)**; **alkaloids (/search?q=alkaloids)**; **terpenoids (/search?q=terpenoids)**; **flavonoids (/search?q=flavonoids)**; **nanoparticles (/search?q=nanoparticles)**

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1. Introduction

Herbal products are of significant importance in traditional medicine. Numbers of plants and plant-based products have been utilized since ancient times. Ayurveda, Traditional Chinese Medicine (TCM), Traditional Korean Medicine (TKM), Kampo, and Unani employ herbal products which have been practiced all over the world for hundreds or even thousands of years. Herbal products have their incomparable advantages, such as abundant clinical experiences, and their unique diversity of chemical structures and biological activities. Herbal products have become some of the most important resources for developing new lead compounds and scaffolds, will undergo continual use toward meeting the urgent need to develop effective drugs and will play a leading role in the discovery of drugs for treating human diseases, especially critical diseases [**1**].

Arthritis is one of the most deceptive diseases globally, with 350 million individuals are currently affected. As per a recent report, one in four adults in the USA suffer from arthritis with severe joint pain [**2**]. Arthritis leads to the breakdown of cartilage which normally protects joints. Arthritis produces an inflammatory riposte as well as hyperplasia of synovial cells. Consequently, extracellular matrix of synovial fluid in the joints develops the sheets in the synovial cells that cause inflammation at joint sites. The pathology of the disease process often indicates that it also damages the articular cartilage and alkalosis of the joints [**3**]. Antiarthritic drugs include idiopathic arthritis, reactive arthritis, psoriatic arthritis, rheumatoid arthritis, septic arthritis, osteoarthritis, and gout are the commonly reported types of arthritis (**Figure 1**).

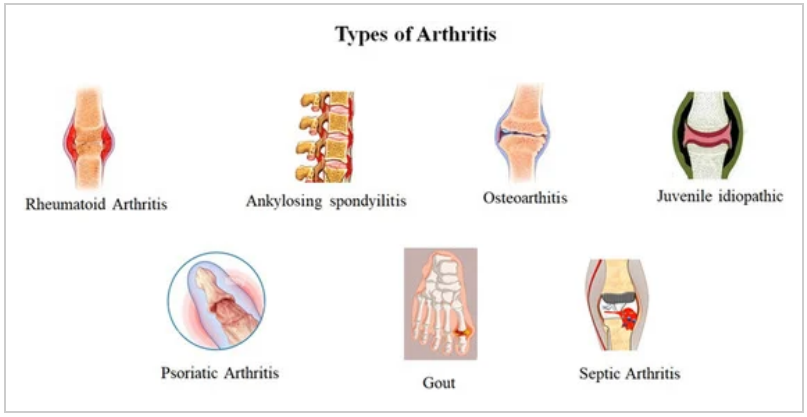

Figure 1. Common types of arthritis reported in the literatures.

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Osteoarthritis (OA) is the commonest form of arthritis, affecting approximately 302 million individuals globally. The most affected areas have been articular joints of the knees, hips, and hands [**4**]. Rheumatoid arthritis (RA) is another type of arthritis affecting the synovial joints and normally produces symmetrical arthritis, leads to considerable socioeconomic impact. RA is one of the most prevalent diseases, affecting approximately 0.5–1% of the world's population. The cause of RA is not certain, but researchers believe that autoimmunity is the major cause The early detection of RA with timely treatment relieves symptoms arising from the RA condition [**5**]. Non-steroidal anti-inflammatory drugs (NSAIDs), including naproxen and aspirin, with rapid onset of action, corticosteroids (e.g., cortisone, dexamethasone etc.), biological agents (e.g., etanercept and infliximab), and disease modifying anti-rheumatic drugs (DMARDs) (e.g., methotrexate, sulfasalazine, leflunomide), either alone or in combination, are the most commonly used treatment strategies for arthritis [**6**]. DMARDs target the immune system, and thus they can also weaken the immune system's ability to fight infections. Furthermore, higher cost and negative impacts on health have limited the use of synthetic drugs in arthritic treatment. Of these synthetic medicines, herbal medicines are also gaining popularity for arthritis treatment, due to fewer side effects.

2. Herbal Antiarthritic Drugs

Herbal products have been widely used as medicine since ancient eras. These natural products have broad chemical diversity, pharmacological specificity, and molecular properties that make them potential candidates for lead structure identification [**7**,**8**]. Thousands of plant isolates possessing antiarthritic (AA) properties have been investigated and reported [**9**]. These plant isolates have been categorized into alkaloids, glycosides, terpenoids, flavonoids, etc. [**10**] In recent years, herbal products showing anti-inflammatory-mediated AA properties have been isolated [**11**,**12**]. These plants have been used either solely, or their extracts or isolates have been used for the treatment of RA or OA. Plant isolate is a pure compound obtained from a plant extract, having a defined structure which is responsible for particular biological activity, and helps to develop new potent compounds. **Table 1** represents numerous plant isolates with their structure and IUPAC names. These plant isolates act through different mechanisms, which are summarized in **Figure 2**.

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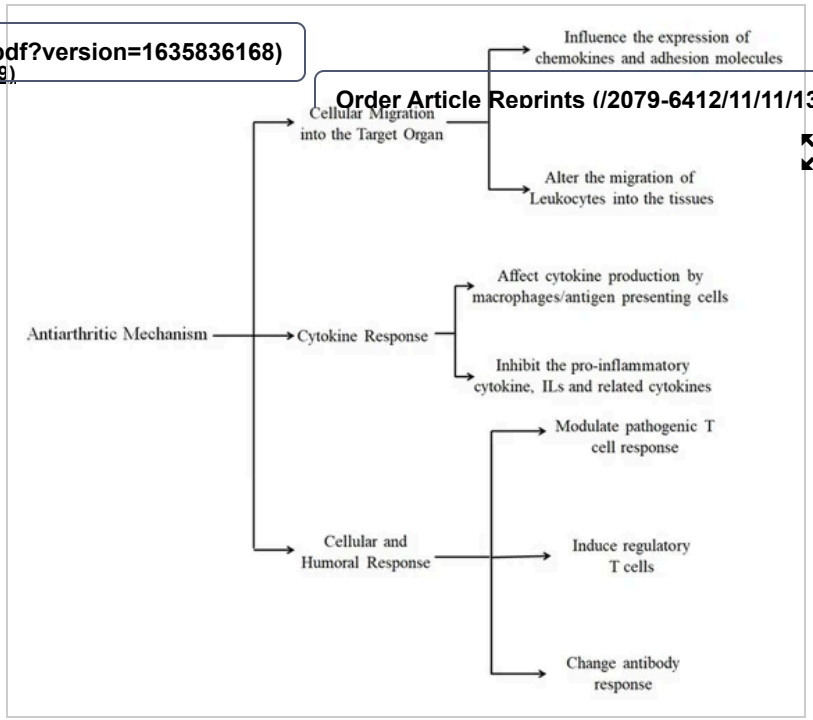

Figure 2. Mechanisms involved in the treatment of arthritis.

Table 1. List of herbal isolates with their molecular formula, structures, and IUPAC names.

2.1. Alkaloids

2.1.1. Montanine

Plants belonging to the *Amaryllidaceae* family have a long history of usage globally, and are found to be a promising therapeutic tool for several human diseases. The plants belonging to this family have long been used as an alternative

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medicine in developing countries. The *Amaryllidaceae* alkaloids are secondary metabolites (alkaloids) of the *Amaryllidaceae* family. Native to Argentina, Brazil, and Uruguay [**13**]. Montanine has structural similarities to *Amaryllidaceae* alkaloids, and its pleiotropic pharmacologic activity raises the possibility of montanine possessing anti-arthritic properties [**14**].

Recently, montanine has received the considerable attention due to its strong anti-inflammatory action, which was isolated from the bulb of the plant *Rhodophiala bifida* (Herb.) through maceration in sulfuric acid 2% (*v*/*v*) [**15**]. The authors reported its significant AA activity by using in vitro effects on lymphocyte proliferation and on invasiveness of fibroblast-like synoviocytes (FLS). Later, the activity of isolate was evaluated on antigen-induced arthritis (AIA) Balb/c mice and collagen-induced arthritis (CIA) DBA/1J mice models. Study results revealed that montanine administration decreased nociception and leukocyte articular migration in the AIA model, and reduced the severity of arthritis and joint damage in CIA model. Histological results revealed considerable improvements in arthritis. The authors proposed that the inhibition of lymphocyte proliferation and decreased FLS invasion was responsible for AA activity. A median lethal dose (LD50) of montanine was reported to be 64.7 mg/kg for male mice and the occurrence of side effects as altered motor activity, decreased respiratory rate, violent body tremors, and clonic convulsions.

2.1.2. Acetylaconitine

3-Acetylaconitine (AAc) is a nitrogen-containing alkaloid, obtained from *Aconitum flavum* and *Aconitum pendulum* (*Ranunculaceae*). Tang et al. isolated AAc from the root of *Aconitum flavum*, and reported its AA activity in mouse and rat models [**16**]. An oral dose of 0.3–0.5 mg/kg of AAc impeded swelling of the hind paw in the formaldehyde-induced rat model, and inhibited the carrageenan-induced edema in the adrenalectomized rat model. Although AAc inhibited acetic acid and histamine-induced vascular permeability, it did not reduce the ascorbic acid content of the adrenal in rats, indicating that AAc did not act through stimulation of the pituitary adrenal axis.

2.1.3. Sanguinarine

Sanguinarine (SA) is a natural plant benzylisoquinoline alkaloid isolated from *Argemone mexicana, Bocconia frutescens, Bocconia frutescens, Chelidonium majus, Macleaya cordata, and Sanguinaria Canadensis*. SA is U.S.A Food and Drug Administration (FDA) approved; it inhibits osteoclast formation, and is recommended for inflammation [**17**]. Ma et al. isolated SA from the roots of *Sanguinaria Canadensis,* and investigated the therapeutic effect of SA against OA [**18**]. Results revealed that SA suppressed catabolic proteases expression in in vitro, in vivo, and ex vivo models. SA suppressed NF-κB and JNK activation, which presented a high level of specificity in repressing the production of catabolic factors. Additionally, SA also

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inhibited IL-1β-induced expression of matrix metalloproteinase (MMPs) 1, 3, and 13. It also suppressed a metalloproteinase and thrombospondin motifs-5 in chondrocytes. These results supported the potential application of SA in OA treatment.

2.1.4. Jatrorrhizine

Jatrorrhizine hydrochloride (JH) is a protoberberine alkaloid reported in many medicinal plants, including *Berberis aristata* and *Coptis chinensis* [**19**]. Qiu and colleagues recently investigated and reported the AA potential of commercially available isolate JH in a CIA rat model [**20**]. The results revealed the suppression of RA in the CIA rat model via an anti-inflammation action, and suppression of bone destruction. Furthermore, the in vitro assay showed inhibition of production of inflammatory mediators, and inhibition of proliferation and migration in MH7A cells. JH was found to suppress tumor necrosis factor-α (TNF-α)-stimulated activation of nuclear factor kappa B (NF-κB) and mitogen-activated protein kinases (MAPKs), leading to suppression of proinflammatory mediators. These results suggested JH as potential compound for AA treatment.

2.1.5. Piperine

Piperine is another alkaloid obtained from black pepper (*Piper nigrum* L.), responsible for the pungent taste, and found in the members of the *Piperaceae* family. *Piper nigrum* L. contains the highest amount of piperine, i.e., from 2% to 9%. *Piper nigrum* L. has been widely used in Ayurvedic and Chinese medicine [**21**]. Bang and colleagues in 2009 reported anti-inflammatory, nociceptive, and AA activities of piperine [**22**]. The AA activity was measured in a CI arthritis model in vivo by measuring the paw volume and weight distribution ratio. The results showed significant reduction of paw volume and weight distribution ratio. The authors also evaluated the levels of IL6, MMPs, COX-2, and PGE2 by ELISA and RT-PCR. An oral dose of piperine between 20 and 100 mg/kg/day for 8 days, inhibited the IL6 and MMP13 expression and PGE2 production. Surprisingly, piperine did not inhibit the expression of NFκB, but did suppress the migration of activator protein 1 (AP-1). Ultimately, on the fourth day, piperine reduced arthritic symptoms. These results suggested the potential of piperine in arthritis treatment.

2.1.6. Capsaicin

Capsaicin is an active component of chili peppers (genus Capsicum), and is produced as a secondary metabolite. It is a chemical irritant for mammals, including humans [**23**]. Ahmed and colleagues investigated capsaicin effects on substrate P (SP) and calcitonin gene-related peptide (CGRP) in the ankle joints and dorsal root ganglia (L2–L6) of adult female Lewis rats [**24**].

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Subcutaneous injection of capsaicin in a dose of 200 mg/kg significantly reduced the level of substrate P (19%) and CGRP (42 %) in the ankle joint of adjuvant-induced arthritic rats. In the ankle joint, capsaicin reduced the SP level by 40%, accompanied by a 40% reduction in inflammatory response. Furthermore, the capsaicin administration reduced the up-regulated levels of sensory neuropeptides in dorsal root ganglia and ankle joints in adjuvant-induced arthritis rats. These findings suggested that capsaicin is useful in arthritis treatment.

2.1.7. Tubastrine

The alkaloid tubastrine, obtained from the marine organism *Aplidium orthium* (Ascidiacea), possesses anti-inflammatory properties [**25**]. Tubastrine isolated from the frozen specimen of *Aplidium orthium* with methanolic acid, followed by chloroform, reduced superoxide synthesis in phorbol-12-myristate 13-acetate (PMA)-stimulated neutrophils in vitro and, in an in vivo study, reduced superoxide levels in a gouty arthritis model [**26**]. Additionally, tubastrine further showed an inhibitory effect on neutrophil infiltration in an in vivo model.

2.1.8. Orthidines

The orthidines (A–F) are a group of marine alkaloids isolated from the same ascidian *Aplidium orthium.* Orthidines (A–D) are benzodioxane orthidines, orthidine E (a cyclobutane dimer of tubastrine), and orthidine F (a biosynthetically unrelated dihydroxanthine derivative) from the frozen specimen of New Zealand *ascidian Aplidium orthium* with methanolic acid, followed by chloroform, and evaluated anti-inflammatory and anti-arthritic activity in a gouty arthritis model [**26**]. Isolated orthidines (A–F) showed the in vitro production of superoxide by PMA-stimulated human neutrophils in a dose-dependent manner with IC_{50s} of 10–36 μM, and this was associated within the inhibition of superoxide production by neutrophils in vivo in a murine model of gouty inflammation.

2.2. Terpenoids

Terpenoids are plant secondary metabolites, extracted from various parts of the plant, such as stalks, fruits, flowers, leaves, and roots. They are colorless liquids with a pleasant smell, and have a high refractive index [**27**,**28**]. The pharmaceutical importance of terpenoids has been proved and well documented in its anti-inflammatory, antibacterial, antiviral, antioxidant, and anti-carcinogenic properties [**29**]. Recently, Carvalho et al., identified and reported 24 terpenoids which were effective in the treatment of inflammation and arthritis [**30**].

2.2.1. Eugenol

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Eugenol is a major phenolic component obtained from the clove bud (*Eugenia caryophyllata*), and constitutes 80–90% of clove oil. Chandrika et al. reported the suppressive effects of eugenol on arthritic symptoms [**31**]. A study was further carried out by Grespan et al. to estimate the AA activity of eugenol in a CIA mouse model [**32**]. The arthritic symptoms were induced with 100 µg of bovine collagen type II (CII) in male DBA1/J mice, and treated with orally administered eugenol (100 µg/mouse) from day 25 to day 40. Eugenol administration significantly decreased the levels of cytokines (i.e., TNF-α, tumor growth factor (TGF)-β, and interferon (IFN)-γ) within the ankle joints. Furthermore, the results indicated that eugenol also inhibited mononuclear cell infiltration into the knee joints of arthritic mice.

2.2. Nimbolide

Nimbolide is a triterpene, which is isolated from the leaves and flowers of the neem plant (*Azadirachta indica*), and has been widely used in treating numerous human ailments. Several bioactive compounds have been isolated from this plant species which exhibit multiple pharmacological effects. Cui et al. performed the AA activity of nimbolide on male albino rats against Freund's adjuvant-induced arthritis [**33**]. A study was carried out to access the AA activities of nimbolide using different in silico and in vivo analytical methods. AA activity of nimbolide (at a dose of 20 mg/kg per day, which was given orally) exhibited a noticeable reduction in edema formation, paw volume, organ indices, and arthritic score, along with considerable improvement in body weight. Histopathological studies revealed the protecting effects of nimbolide towards joints and inflammation. The outcomes of the study showed that nimbolide treatment inhibited inflammation by decreasing the proinflammatory cytokines (i.e., TNF-a, IL-6, IL-1b, and IL-10) manifestation in arthritic rats. Furthermore, nimbolide normalized the increased levels of iNOS, P-IkBa, Nf-kb, cox-2, and IKKa in treated rats.

2.3. Bartogenic Acid

Bartogenic acid (BA) is isolated from the fruits of the *Barringtonia racemosa* Roxb. (Lecythidaceae) plant [**34**]. A study was performed by Patil et al. in order to evaluate the AA activity of BA [**35**]. BA was isolated from the methanolic extract of fruits of *Barringtonia racemosa*. The in vivo results revealed noteworthy AA activity of BA against CFA-induced arthritis in rats by reducing serum markers, such as rheumatoid factor and C-reactive protein. BA protected against primary and secondary arthritis lesions with a dose of 2, 5, and 10 mg kg^{-1} day^{-1}. It also normalized the raised WBC counts and increased hemoglobin counts, and reduced erythrocyte sedimentation rate in arthritic conditions. The possible mechanism to improve Hb count by BA was due to increased response of the bone marrow erythropoietin. BA also protected the rats from CFA-induced radiographic changes.

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2.2.4. Cannabidiol

Cannabidiol (CBD) are meroterpenoids, terpenophenolic compounds which are isolated from the plant *Cannabis sativa* L., belonging to the *Cannabaceae* family, and cultivated worldwide. This plant contains a number of phytoconstituents including amides, amines, phytosterols, phenolic compounds, carbohydrates, terpenes, and fatty acids and their esters, along with CBD as main active constitute [**36**].

Several reports have clarified that CBD showed anti-inflammatory activity by inhibiting proliferative responses of T lymphocytes, nitric oxide (NO) production by macrophages, and suppression of macrophage function and antigen presentation. Malfait et al. demonstrated the AA therapeutic potential of cannabidiol in murine collagen-induced arthritis [**37**]. Arthritis was developed by bovine type II collagen (CII), and immunized completely against Freund's adjuvant (CFA) in DBA/1 mice at the dose of 100 µg. Cannabidiol was found to be equipotent in both models (chronic relapsing CIA and in acute CIA), and the optimal dose of cannabidiol was found to be 5 mg/kg i.p. per day, or 25 mg/kg orally per day. Joints were protected against severe damage, and showed significant IFN-γ production and diminished CII-specific proliferation. Ex vivo results showed a decrease in TNF-α release and diminished CII-specific proliferation and IFN-g production by knee synovial cells in CBD-treated mice. A dose-dependent suppression of lymphocyte proliferation was also observed by CBD in in vitro studies. Additionally, cannabidiol suppressed the lipopolysaccharide-increased serum TNF level in C57/BL mice. These combined data showed immunosuppressive and anti-inflammatory actions which mediated the A effect of CBD on CIA. A patent has also been filed describing the identification and use of CBD to treat inflammatory diseases [**38**].

2.2.5. Curcumin

Curcumin is the most active phytocomponent of *Curcuma longa* Linn, which belongs to the *Zingiberaceae* family, and is commonly cultivated in the region of south Asia. *Curcuma longa* is widely used in traditional Indian Ayurveda medicine as a popular home remedy, and its paste is applied with slaked lime for the treatment of inflammation and wounds [**39**]. Curcumin has received much interest in the scientific world due to its excellent pharmacological activities, which have been shown to target multiple signaling molecules at the cellular level. Curcumin has been known to possess AA effects in humans with OA and RA [**40**].

Huang et al. evaluated the anti-RA effect of curcumin in a CIA-induced DBA/1J mice model. A 50 mg/kg of curcumin was injected i.p. in the mice model, and the B cell-activating factor belonging to the TNF family (BAFF), IL6 and IFNγ production in serum were measured. Results revealed a decreased production of BAFF, IFNγ and IL-6 in serum. Furthermore, western blot

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analysis was also performed to measure IFNγ-related signal transducers and activators of transcription 1 (STAT1) signaling in B. Curcumin decreased IFNγ-induced BAFF expression, STAT1 phosphorylation, and nuclear translocation after curcumin treatment [**41**]. Kuncha and colleagues reported the potentiate effect of curcumin with low dose of prednisolone against CFA-induced arthritis in a rat model [**42**].

An interesting study was performed by Yu et al., demonstrating the anti-neuroinflammatory response of curcumin in lipoteichoic acid (LTA)-stimulated BV-2 microglial cells [**43**]. Results revealed that curcumin inhibited the secretion of inflammatory cytokine NO and TNF-α, prostaglandin E2 (PGE2), and also inhibited COX-2 and iNOS expression. Additionally, curcumin also suppressed LTA-induced phosphorylation of MAPK expression. In LTA-stimulated microglial cells, curcumin inhibited hemeoxygenase-1(HO-1), which reversed the inflammatory mediator release, and produced their effect against neurodegenerative disorder neuroinflammation.

2.3. *Flavonoids*

Flavonoids are polyphenolic compounds isolated from plants and found in grains, fruits, flowers, vegetables, bark, stems, and seeds. Flavonoids have been shown to possess anti-inflammatory properties, and these plant products have been widely used traditionally in the treatment of arthritis [**44**].

2.3.1. Quercetin or 3,5,7,3′,4′-Pentahydroxy Flavone

Quercetin (QTN) is a flavonoid obtained from apples, buckwheat, onions, and citrus fruits. Recently, Yuan et al. investigated and reported the mechanism of AA activity of QTN [**45**]. QTN significantly reduced ankle diameter and arthritic scores in adjuvant-induced arthritis (A42A) in a mouse model. The study revealed that QTN endorsed apoptosis of activated neutrophils, and inhibited neutrophil infiltration. Additionally, QTN inhibited ROS-mediated neutrophil extracellular traps (NETs) formation and autophagy. These findings suggested that QTN may be a potential agent for RA treatment by inhibiting neutrophil activities. QTN (30 mg/kg) oral administration showed a decrease in clinical sign of arthritis in a chronic rat (AA) model [**46**]. Gardi et al. showed a decrease in IL-1b level, monocyte chemotactic protein-1 (MCP-1) level, and also restored plasma antioxidant capacity in rat adjuvant arthritis after oral administration of QTN (150 mg/kg) [**47**].

Gaikwad et al. reported anti-inflammatory activity of ethanol extract of flowers of *madhuca indica* against formaldehyde-induced inflammation, carrageenan-induced inflammation, and cotton pellet granuloma in models of rats. Results revealed a superior dose-dependent anti-inflammatory action of ethanolic extract of *m. indica*, as compared to the reference drug diclofenac sodium in a formaldehyde-induced inflammation model [**48**]. The study was further extended by Tang and colleagues

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in 2021, who isolated QTN from methanolic leaves extract of *madhuca indica*, and evaluated for AA activity against FCA-induced arthritis in rats (strain: Wistar). The in vivo results demonstrated a significant decrease in paw volume, joint diameter, and paw withdrawal threshold after QTN (10 and 20 mg/kg) treatment. The AA activity of QTN revealed reduced elevated inflammatory release (Ikβα, P2X&, COX-2 and NF-κβ), oxido-nitrosative stress, and pro-inflammatory cytokines (TNF-α and ILs) in experimental rats [**49**].

QTN was more effective alone than methotrexate, or in combination with methotrexate, to reduce joint inflammation in mice, and provided the highest protection against arthritis. The mechanisms included reduction of TNF-α, IL-1β, IL-17, and monocyte chemoattractant protein-1 (MCP-1) levels [**50**].

2.3.2. Resveratrol

Resveratrol (Res), a natural flavone, is widely present in medicinal plants including grape, cranberry, mulberry, pistachio, and peanut. The AA activity of Res was evaluated against a CFA-induced rat model by Chen and colleagues in 2013. Res was showed to inhibit the mRNA expression of IL-1β and TNF-α and, ultimately, IL-1β and TNF-α level after given through intragastric gavage (i.g. 10 mL/kg/day). Res stimulated synoviocytes, and the protein expression levels of p-ERK1/2 via protein kinase C (PKC) [**51**].

It has been reported that resveratrol inhibits the enzymatic activity of COX-1 and COX-2. Chen et al. investigated the AA effect of resveratrol on CFA-induced arthritis in a rat model [**52**]. The results revealed a significant paw swelling reduction with decreased arthritis scores (10 or 50 mg/kg, i.g.). Additionally, resveratrol suppressed the production of COX-2 and PGE2 inflammatory mediators. The study further revealed the histopathology improvement by resveratrol in AA rats.

Co-administration of Res and piperine significantly decreased the paw swelling and ameliorated the histopathological changes. The combined treatment highly reduced the serum TNF-a, IL-1b, thiobarbituric acid reactive substances (TBARS), and nitrate/nitrite (NOx). Moreover, a nearly negative expression of NF-κB p65 in the synovial tissue was observed by co-administration of piperine with Res. Results of the combination treatment were comparable to that of diclofenac treatment [**53**].

2.3.3. Kaempferol

Kaempferol (KAE), a natural flavanol, chemically known as 3,4′,5,7-tetrahydroxyflavone, is found in numbers of edible plants such as beans, tea, kale, broccoli, and spinach. KAE is used as a traditional medicine for numerous inflammatory disorders. Studies revealed that KAE reduces COX-2 levels in RAW 264.7 cells, and inhibits ROS production via inhibition of iNOS and TNF-α protein expression. KAE also inhibits IL-4, C-reactive protein (CRP) expression and NF-κB in liver cells

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[54,55]. Yoon et al. reported that KAE produces AA activity by inhibiting the proliferation of both unstimulated and IL-1β-stimulated FLS in addition to the mRNA and protein expression of MMP-1, MMP-3, PGE2, and COX-2 induced by IL-1β **[56]**.

2.3.4. Chebulanin

Chebulanin is a natural polyphenolic compound isolated from the fruits of *Terminalia chebula retzius* (*TC*). *Terminalia chebula retzius* (*TC*) is widely used in medicine in Asian countries for its anti-microbial, anti-inflammatory, antioxidant, and AA properties. Zhao and colleagues investigated the chebulanin function as an AA agent in a CIA-animal model using DBA/1 mice **[57]**. Chebulanin was isolated from dry fruits of *Terminalia chebula retzius* with a 70% acetone solution (1:10, *w*/*v*) at room temperature (25 ± 2 °C). The authors measured the expression of inflammatory cytokines by immunohistochemical staining, and also performed a histopathological evaluation of the joints. Micro-CT was also performed to detect bone destruction and erosion. The results of above studies revealed the improved dose-dependent (oral dose of 40 mg/kg, 80 mg/kg or 160 mg/kg daily for 28 days) expression of IL-6, TNF-α, MMP-3, and COX-2 in joints and, ultimately, severity of arthritis. Additionally, histopathological studies revealed tissue improvement. Micro-CT results showed the dose-dependent reduction in cartilage destruction and bone erosion. These results confirm the potential role of chebulanin as a strong therapeutic agent for the treatment of RA. Recently, Liu et al. also confirmed the AA activity of chebulanin via inhibiting NF-κB and MAPK activation in a collagen-induced arthritis (CIA)mouse model **[58]**. Chebulanin significantly decreased the arthritic scores, paw swelling and IL-6 and TNF-α level in mice after being orally gavaged (80 mg/kg) daily for a total of 21 days. Moreover, chebulanin reduced the levels of excised phosphorylated (p)-p38, c-JUN, p-p65, N-terminal kinase (p-JNK), and phosphorylated NF-κB inhibitor alpha (p-IκBα), but did not alter extracellular-signal regulated kinase, which is implicated in many pathological conditions, including arthritis.

2.3.5. Ellagic Acid

Ellagic acid (EA) is a polyphenol bioactive compound richly existing in berries (strew berry, raspberry, and cloudberry), almonds, grapes, walnuts, and pomegranates **[59,60]**. Shruthi et al. isolated the ellagic acid from the methanol leaf extract of the plant *Kirganelia reticulate,* and tested its AA activity via in vitro, in vivo, and in silico assays **[61]**. The in vitro assay of EA showed maximum percentage inhibition of protein denaturation, membrane stabilization, and proteinase inhibitory action, which were observed at 250 µg/mL. The in vivo studies of EA against the formaldehyde-induced paw edema showed inhibition of cytokines and leukotriene infiltration, reduced paw edema volume, protected synovial membranes, and cartilage damage at

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both 100 µg/mL and 250 µg/mL concentration. The possible proposed mechanism was inhibition of hypoxia-inducible factor (HIF-2α). Body weight, paw edema volume, and the movements of rats, were also studied, which showed a protective effect of EA similar to standard aspirin. The in silico study of EA revealed that it forms four hydrogen bonds with amino acid residues in the active pocket of Hypoxia-inducible factor (HIF-2α). The EA completely enfolded in the entire active pocket of HIF-2α, as compared to aspirin, and inhibited the activity of HIF-2α protein, thereby reducing remarkable anti-arthritic activity. The acute oral toxicity study of EA was also performed in albino rats via the OECD Organization of Economic Co-operation and Development guidelines (OECD No. 423). The results of toxicity studies revealed absence of any toxic effect up to 2500 mg/kg body weight.

Umar et al. investigated the combinatory effect of methotrexate and EA on the CIA-Wistar rat method. CIA rats were treated with solely methotrexate (1 mg/kg/week) and EA (60 mg/kg) daily, and the combination of methotrexate and EA for a period of 28 days [**62**]. Results revealed that the combination of methotrexate and EA potentiated the antiarthritic (decrease of hind paw volume and scoring) and the antioxidant effect (GSH and catalase), as well as suppression of lipid peroxidation. Combination therapy of methotrexate and EA significantly inhibited the development phase of arthritis, which is supported by histopathological and attenuation of pro inflammatory cytokines.

2.3.6. Rosmarinic Acid

Rosmarinic acid is a polyphenol, present in a number of herbs, including rosemary (*Rosmarinus officinalis* L.), mint (*Mentha arvense* L.), sage (*Salvia officinalis* L.), and basil (*Ocimum basilicum* L.). In 1958, it was first isolated and characterized by the Italian chemist Scarpatti from rosemary (*Rosmarinus officinalis*), and hence given its name rosmarinic acid [**63**]. Recently, Wei et al. isolated rosmarinic acid from *Rosmarinus officinalis* methanolic leaf extract, and reported its AA activity against CFA-induced arthritis in rats [**64**]. Oral administration of rosmarinic acid at a dose of 30 and 60 mg/kg exerts significant reduction in hind paw volume and various other arthritic symptoms, i.e., inflammation and joint stiffness. Rats treated with rosmarinic acid in a dose of 60 mg/kg, i.p improved locomotor movement from days 21 to 35. Additionally, rosmarinic acid also decreased TNF-α levels in serum in a dose-dependent manner in treated rats. Rosmarinic acid decreased the levels of inflammatory mediators TNF-α in treated animals. On the basis of these outcomes, the authors suggested rosmarinic acid as an encouraging candidate for the treatment of arthritis. Acute toxicity study of rosmarinic acid (according to OECD No. 423 guidelines) showed no sign of toxicity or onset of toxicity up to the dose of 2000 mg/kg body weight of albino rats.

2.3.7. Gallic Acid

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Gallic acid (GA) is a natural polyphenol, present in gall nuts, oak bark, apple peels, sumac, grapes, tea leaves, and green tea. Anti-inflammatory, anti-rheumatic, anti-tumor, and pro-apoptotic activities of GA have been well documented. Shi et al. reported that tumor-like FLSs cells could migrate to cartilage and bone, producing pannus and accelerate the secretion of pro-inflammatory cytokines, chemokines, and MMPs [**65**]. GA has been found to inhibit cytokines, chemokines, and MMPs. Yoon et al. reported that GA triggers the apoptosis of FLSs cells in ≥10 μM concentration, and regulates the production of Bcl-2, Bax, p53, and pAkt in western blot analyses, and in the mRNA expressions analysis. Furthermore, GA also showed dose-dependent suppression of cytokines (IL-1, IL-6), chemokines (CCL-2/MCP-1, CCL-7/MCP3), COX-2, and MMPs-9 from RA FLS [**66**]. GA regulated apoptosis related protein expressions (i.e., fibroblast-like synoviocytes from patients with rheumatoid arthritis; RA FLS), and reduced the expression of pro-inflammatory genes in RA FLS. On the basis of these outcomes, the authors suggested that GA utilizes pro-apoptotic and anti-inflammatory therapeutic options for RA treatment. The acute toxicity of GA showed LD50 values greater than 2000 mg/kg in albino mice. However, at a higher dose (900 mg/kg) of GA up to 28 days did not alter the behavior, morphology, or histopathological parameters in mice.

2.3.8. Chlorogenic Acid

Chlorogenic Acid (CGA) is the most abundant phenolic acid, naturally occurring in tea and green coffee extracts. CGA. Chauhan and his team investigated the AA activities of CGA in an adjuvant induced-arthritis model using male Wistar rats [**67**]. At a dose of 40mg/kg, CGA controlled both total (CD3) and differentiated (CD4 and CD8) T-cell count, and effectively suppressed CD80/86, compared to ibuprofen. Flow cytometry analysis results demonstrate suppression of Th1 cytokines and elevation of Th2 cytokines by CGA. Fu and colleagues reported that CGA obstructed arthritis progression, and inhibited BAFF and TNF-α production in serum in a CIA-mice model [**68**]. Mechanistically, CGA showed constraints of TNF-α-induced BAFF expression, and reduced the DNA-binding activity of NF-κB to the BAFF promoter region in MH7A cells. These results suggested the potential of CGA as AA agent. Group of animals treated with CGA showed no abnormal behavior or mortality up to the dose of 2000 mg/kg, which showed the safety of CGA, even at high doses.

2.3.9. Ferulic Acid

Ferulic acid (FA) is the most common compound, present in numerous plants, particularly in grains, including rice and corn. FA exhibits free radical scavenger activity, and increases the expression of antioxidant proteins via the activation of NF-kB and COX-2, as well as inhibiting iNOS [**69**]. These properties of FA encouraged Zhu and colleagues to investigate FA effects in the treatment of CFA-induced arthritis in rats [**70**]. The authors also investigated whether the effect, if present, is due to the

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inhibition of the JAK/ STAT pathway or not. Results revealed that at an oral dose of 25 and 50 mg/kg of FA administered to CFA-induced arthritic rats showed significant reduction in arthritic index, ESR levels, and the percentage of lymphocytes. Both rheumatoid factor (RF) and C-reactive protein (CRP) are also reversed after FA treatment, and normalized the physiological condition. FA treatment also reduces the level of TNF-α, JAK2 levels, TGF-β, STAT-3, and STAT-4 levels. These findings suggested the potential use of FA in arthritic treatment by inhibition of the JAK pathway. Oral administration of FA showed low toxicity with an acute LD50 value of 3200 mg/kg in mice, while LD50 values were 2445 mg/kg and 2113 mg/kg for male and female rats, respectively.

2.3. Brazilin

Brazilin is a naturally occurring active compound (red dye) obtained from the wood of various plants such as *Caesalpinia violacea*, *Haematoxylum brasiletto*, *Brazilin Paubrasilia echinata* and heartwood of *Caesalpinia sappan* [**71**]. Jung et al. isolated brazilin from ethyl acetate extract of the heartwood plant *Caesalpinia sappan* L., and investigated its AA activity. HPLC was utilized to purify isolated brazilin, and its confirmation was performed using mass spectrometry and $^{1}H/^{13}C$ NMR analysis [**72**]. A type II CIA mouse model was utilized for the determination of brazilin anti-rheumatoid activity. A 10 mg/kg body weight of purified brazilin and a 3 mg/kg body weight of methotrexate were administered intraperitoneally, and pro-inflammatory cytokines and stress enzyme markers were monitored. Results revealed a significant reduction in inflammatory cytokines, acute inflammatory paw edema, and arthritis index score in CIA-mice model. Additionally, the bone mineral density was improved adequately with both brazilin and methotrexate administration. The microstructural examinations showed joint prevention, bone formation, and prevention of surface erosion after brazilin administration. These results showed protective efficacy of brazilin in a CIA mouse model, and suggested that it would be useful to treat rheumatoid arthritis.

2.4. Plant Sterols

Beta-Sitosterol

Beta-sitosterol is a “plant sterol ester” found in fruits, vegetables, nuts, and seeds. It is commonly used for lowering cholesterol levels and improving symptoms of an enlarged prostate [**73**]. Liu et al. evaluated the effects of β-sitosterol of immune-regulation on macrophages and its potential role in rheumatoid arthritis (RA) [**74**]. β-sitosterol in a dose of 20 or 50 mg/kg i.p. boosts immunization of CIA in mice models. β-sitosterol-treated M1-polarized bone marrow-derived macrophages (BMDMs) reduced expression of CD86, IL-1b, iNOS, and MHCII by 87.1, 47.1, 50.2, and 31.3%, respectively. In CIA mice, β-

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sitosterol inhibited the production of proinflammatory cytokines, and reduced the levels of collagen-specific antibodies (IgG and IgG1). Further, these results suggested the potential application of β-sitosterol in RA therapy.

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3. Nano-Formulation of Isolated Compounds

Nanotechnology has been widely used for the treatment of severe diseases, with the objective of increasing efficacy and safety of active ingredients [**75**,**76**]. Nanocarriers have numerous advantages, including controlled and site-specific drug delivery, which minimizes unwanted side effects [**77**,**78**]. Nanocarriers have also gained much attention for the delivery of plant extracts and isolates. Several reports demonstrate the increment in AA activity of herbal extracts through utilizing nanotechnology by increasing their bioavailability. The details of plant isolates with their nanoformulation, method of preparation, and average particle size is given in **Table 2**.

Table 2. Plant isolates with their nano-formulation for antiarthritic or antioxidant activity.

Piperine-loaded solid lipid nanoparticle (SLN) were prepared through the melt emulsification method, and evaluated for particle size (128.80 nm), entrapment efficiency (78.71%), and zeta potential (−23.34 Mv). The prepared SLN was administered orally and topically to CFA-induced arthritic rats. An ex vivo study using Franz diffusion cells indicates that piperine from the SLN gel formulation accumulates in the skin. TNF α was significantly decreased by piperine-SLN, as compared to the arthritic control group, which may be attributed to the selective accumulation of piperine-SLN in inflamed sites thus reducing the secretion to TNF α from the activated macrophages. Histopathology studies revealed that piperine-SLN showed minimal infiltration of inflammatory cells and connective tissue proliferation, as compared to a control group, which showed moderate infiltration of inflammatory cells and connective tissue proliferation [**79**].

Sarwa and colleagues, in 2013, prepared and reported capsaicin-loaded transfersomal vesicular system for topical application in experimental arthritic rats [**80**]. Capsaicin-loaded transferosomes were prepared through the conventional thin

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film hydration method, and evaluated for numerous physical properties including morphology, size and size distribution, zeta potential, and entrapment efficacy. The prepared transferosomes were nano sized (94 nm), with sufficient structural flexibility and negative surface charge (−14.5 mV). Furthermore, capsaicin-loaded transferosomes were compared to marketed Thermagel (standard) gel for antiarthritic activity. The results revealed enhanced permeability of transferosome formulations as compared to the marketed Thermagel formulation, and thus led to improved therapeutic concentration of the capsaicin at the desired site, ultimately improving the antiarthritic and anti-inflammatory activity of transferosome formulations over Thermagel formulation.

Jabbari and colleagues investigated the effects of encapsulated eugenol with chitosan nanoparticles on a neonatal CIA-rat model [**81**]. Eugenol-entrapped chitosan nanoparticles (Eug-CNPs) were prepared through the solvent dispersion method, and evaluated for anti-oxidative stress (malondialdehyde for assessment of lipid peroxidation) by an assay kit, FOXO3 protein as an antioxidant up-regulating by western blotting, and expression of the TGF-β and CCL2/MCP-1 genes by real-time PCR evaluation, supported by a cartilage histopathology analysis. Results revealed that Eug-CNPs significantly decreased the serum level of malondialdehyde and FOXO3 protein expression, in comparison to the control group. Additionally, Eug-CNPs decreased the expression of TGF-β and MCP-1 genes, and a significant positive correlation was observed between MCP-1 and TGF-β. Eug-CNPs also alleviated the symptoms of joint inflammation, synovial hyperplasia, and cartilage damage caused by the RA.

QTN was entrapped in cadmium telluride quantum dots (TGA-CdTe QDs) for enhancing its AA activity against adjuvant-induced arthritic in Wistar rats. Treatment with QTN-entrapped TGA-CdTe QDs (QDs-QE) reduced the expressions of lipid peroxidation, and improved antioxidant enzymes activity superoxide dismutase (SOD). Prepared QDs reduced the level of catalase (CAT), glutathione (GSH), and glutathione peroxidase (GPx) in paw tissue. Histopathology studies revealed the cartilage regeneration in arthritis-induced rats after QDs-QE treatment. These outcomes revealed QDs-QE have the potential ability to treat arthritis in rheumatic complications [**82**]. The QDs-QE complex showed improved AA activity at low concentrations via free radical quenching of QDs-QE by antioxidant enzymes, while QE showed AA potential only at the higher concentration. Furthermore, QDs, as nanocarrier of QE, exhibited enhanced AA effect even at a lower concentration of the drug. These findings suggested the utilization of QDs of QE as a nanocarrier to enhance the potential of QE for AA activity. Furthermore, Gokhale et al., developed QCT loaded nano-emulsion (NE) gel using spontaneous emulsification techniques for effective RA management [**83**]. The effect of QCT-NE on the production of inflammatory cytokines TNF-α was investigated on RAW264.7 cells. Results showed the significant inhibition of TNF-mediated inflammation, cartilage destruction, and lastly delay in arthritis progression. The inhibition of paw volume by QCT-NE gel was up to 51.13 ± 1.35 mm, as compared to the control

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group of 71.21 ± 0.33 mm. These results confirmed that QCT-NE gel will be a promising alternative in rheumatic complications via topical route.

Introduction

Recently, Zhang and his team members (2020) evaluated β-sitosterol-loaded solid lipid nanoparticles (SLN) against CFA-induced arthritis in rats. β-sitosterol-loaded SLNs (β -sitosterol-SLNs) were prepared through double emulsion solvent displacement and cytokine levels were measured, which showed reduced expression levels of TNF-α, IL-2, IL-6, IL-16, IL-17, but increased IL-10 and transforming growth factor beta (TGF-β) levels [**84**]. A significant reduction of paw edema and arthritic index were reported by prepared β-sitosterol-SLNs. A significantly reduced level of COX-2, PGE2, VEGF, and NF-κB were reported with β-sitosterol-loaded SLNs. These results concluded that β-sitosterol-SLNs showed a potent antiarthritic effect via suppression of NF-κB and activation of the HO-1/Nrf-2 pathway.

A mixed micellar nano-system of Res was developed using different ratios of poloxamer 188 (Pluronic® F-68) and poloxamer 407 (Pluronic® F-127) through simple thin film hydration for the localized treatment of arthritis [**85**]. The optimized formulation (MM3) composed of P188: P407 in a ratio of 2:1 attained the most compromised properties (Particle size = 52.97 ± 4.52, encapsulation efficiency = 76.20 ± 4.51 and release efficiency = 76.26 ± 6.25), and then coated with poly-lactic acid (PLA). PLA-coated MM3 showed utmost anti-arthritic activity over MM3, followed by drug suspension in CFA-induced arthritis in rats after intra-articular (i.a.) injection. This study demonstrated that intra-articular administration of the designed Res-loaded mixed micellar nano-systems reduced the severity of cartilage lesions and synovial inflammation in the experimental arthritis model, and proved the success of this site-specific restorative/anti-inflammatory treatment for combating the progress of rheumatoid arthritis.

Kaempferol (KAE), a strong antioxidant flavonoid compound, showed limited clinical application, due to its poor dissolution property. Tzeng et al. prepared kaempferol-entrapped Eudragit E100 nanoparticle (KAEN) through a nanoprecipitation technique to resolve the dissolution problem [**86**]. Prepared KAEN effectively increased the dissolution percentage by particle size reduction, high encapsulation efficiency, amorphous transformation, and hydrogen-bond formation with excipients. The antioxidant activity assays showed that the KAEN retained potent antioxidant activity after the nanoparticle engineering process, and showed better antioxidant activity than KAE dissolved in water ($p < 0.05$). These findings suggested that KAEN could be a low-dose alternative to KAE in the treatment of arthritis.

Yücel et al. prepared and reported rosmarinic acid-loaded ethosomes (ETHs) and liposomes (LPs), and evaluated their potential by determining rosmarinic acid penetration from ETHs and LPs in comparison with rosmarinic acid solution through the abdominal skin of mice [**87**]. ETHs were prepared through mechanical dispersion, while LPs were prepared through dry film

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hydration. Both formulations were optimized and characterized, and ex vivo permeation studies were performed mouse abdominal mucosa, which showed enhanced permeation of ETHs over rosmarinic acid solution and LP formulations. Antioxidant activities such as lipid peroxidation and 2-deoxyribose degradation directed by specific and non-specific hydroxyl radicals and the inhibitory effects of formulations on collagenase and elastase enzymes were also measured and reported, showing improved activity of rosmarinic acid loaded ETHs and LPs.

Deligiannakis et al. introduced “nano-antioxidant” with antioxidant-functionalized silica nanoparticles (SiO_2 NPs) and radical scavenging capacity (RSC) of GA [**88**]. GA was covalently grafted over well-characterized SiO_2 NPs of various sizes (8–50 nm), and verified by FTIR spectroscopy and thermogravimetric analysis. Prepared hybrid SiO_2-GA NPs claimed a first proof-of concept of engineered reused, low-cost nano-antioxidant materials capable of scavenging 2,2-diphenyl-1-picrylhydrazyl ($DPPH^{\bullet}$) radicals via fast H-atom transfer reactions are presented. The improved free radical scavenging capacity of SiO_2-GA NPs over plain GA could be utilized in antioxidant-mediated arthritic treatment.

CGA-entrapped gold nanoparticles (CGA-AuNPs) were prepared through novel green synthesis without the use of other chemicals, and their anti-inflammatory efficacy was validated both in vitro and in vivo [**89**]. The prepared CGA-AuNPs were spherical in shape, with an average diameter of 22.25 ± 4.78 nm. CGA-AuNPs inhibited pro-inflammatory cytokines and other inflammation-related genes (including MMPs and Ninj1), and exhibited enhanced anti-inflammatory effects on NF-κB-mediated inflammatory over plain CGA, indicating that functionalization or the combination of AuNPs with green reductants, which are known to have therapeutic or preventive properties, can provide a new strategy for the development of novel anti-inflammatory-mediated anti-arthritic agents. These results recommended further clinical studies to ascertain the in vivo efficacy of CGA-AuNPs for anti-inflammatory or anti-arthritic activities.

ferulic acid loaded nano-emulsion (FA-NE) based gel was prepared by Harwansh et al., using a spontaneous nano-emulsification method to enhance permeability and maximum antioxidant activity of FA against UVA-induced oxidative stress in rats [**90**]. The FA-NE was prepared by oil (isostearyl isostearate), aqueous system and Smix [surfactant (labrasol), and co-surfactant (plurol isostearique), respectively. Prepared FA-NE was characterized and evaluated for ex vivo skin permeation and in vivo UVA protection activity. The results revealed a sustained-release profile, better permeability and UVA protection activity, as compared to conventional dosage form. These results may be attributed towards increased solubility of the drug and enhanced permeability from nano-emulsion. The prepared nano-emulsion was suggested as a promising nanocarrier for topical delivery of FA, in response to better antioxidant activity in a sustained manner.

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Curcumin's solubility and stability at physiological condition hampered its potential in clinical conditions. Renewable polymer-based nano-emulsion (~234 nm) and nano-emulsion (~268 nm) was employed for increasing its solubility and stability [**91**,**92**]. Zheng and colleagues prepared curcumin-loaded nano-emulsions (CM-Ns) using a high-pressure homogenizing method for the treatment of RA. The prepared CM-Ns were evaluated for particle size and morphology, and also studied for in vitro drug release. The diameter of the prepared CM-Ns was found to be 150 nm, with well-encapsulated curcumin in the Ns, without degradation in simulated GI conditions. Prepared CM-Ns showed an augmented area under the curve (AUC) and Cmax, and decreased the level of TNF-α and interleukin-1β more firmly in both synovial fluid and blood serum, as compared to the plain drug [**93**]. The prepared CM-Ns appeared to be a promising system that allowed RA therapy with curcumin to be converted from IV to oral administration.

4. Conclusions

Herbal isolates, referred to as "secondary metabolites", have shown tremendous pharmacological activities, and thus are in use worldwide as medicines or supplements. Through knowing the molecular structures of isolate compounds, attempts could be made to synthesize the desired or more potent compounds. Herbal compound isolates, including alkaloid, terpenoids, flavonoids, and polyphenols, have been reported to possess AA activities. These plant isolates are easy to obtain, and produce remarkable AA activity. However, isolation from plants is still a challenging task, and several researchers are purchasing isolated compounds for their studies. Recently, the number of herbal-based products available in the market for the treatment of arthritis have increased; however, none of them contain pure isolates, but instead contain either mixtures of crude drugs or plant extracts. The AA activity of isolated compounds may be further aggravated by utilizing nano-formulations, possibly due to consequential enhancement in aqueous solubility/ bioavailability and the possibility for site-specific drug release.

Author Contributions

Conceptualization, A.V.; formal analysis, P.K.G.; resources, J.M.R.; writing—original draft preparation, A.V. and S.J.; writing—review and editing, K.K.B. and J.M.R.; supervision, K.K.B.; funding acquisition, K.K.B. and J.M.R. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

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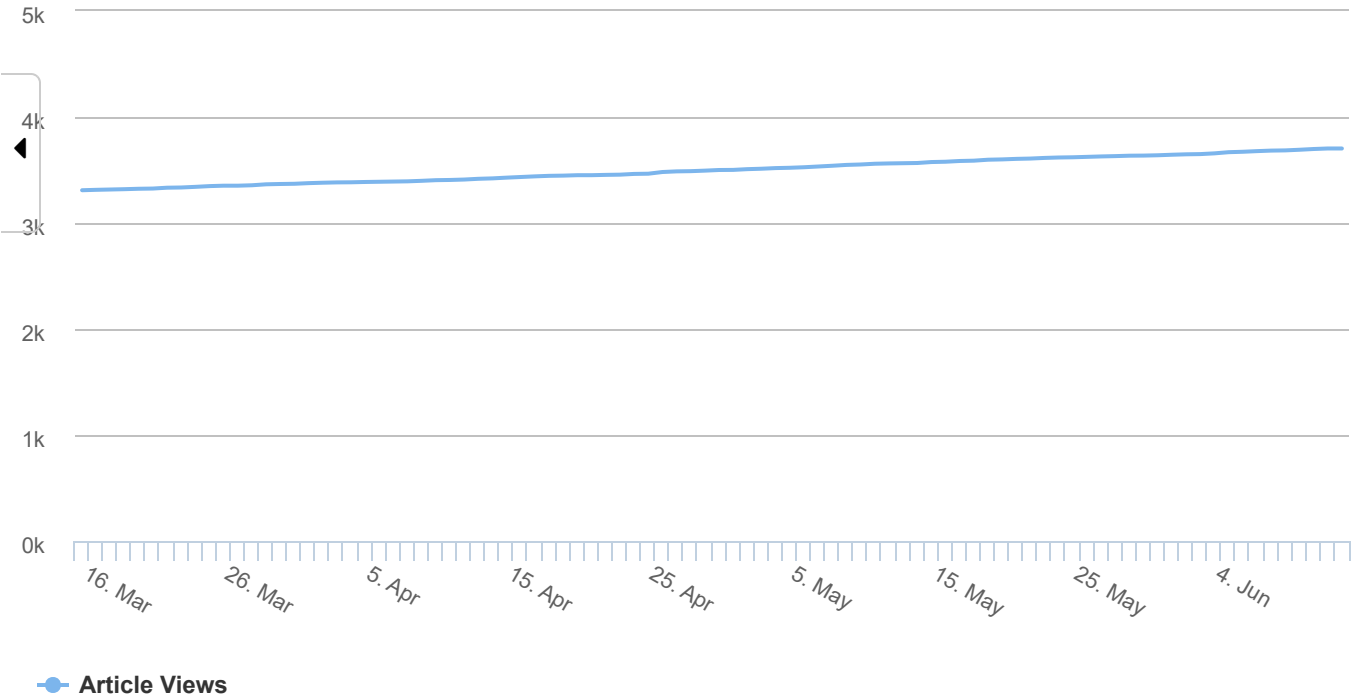

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Nanocarriers for Alzheimer's disease: Research and patent update

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ABSTRACT

Alzheimer's disease (AD) is one of the most progressive neurodegenerative disorders resulting in cognitive and behavioral impairment in individuals beyond 65 years of age. It is distinguished by deposits of extracellular amyloidal protein intracellular and neurofibrillary tangles resulting in senile plaques. Significant advancement has been made in AD therapeutics; however, most of the treatment approaches are based on attenuating symptoms, implying that AD is still an insolvable neurodegenerative illness. Though an enormous number of drug moieties were already screened for different molecular targets of AD, only few of them (N-methyl D-aspartate receptor antagonists and acetylcholinesterase inhibitors) are currently implied for efficacious clinical treatment. Though these medications slow down the development of the disorder and give symptomatic relief; yet they are unsuccessful in achieving a proven cure. Nonetheless, targeted drug delivery of these medications to the Central nervous system (CNS) manifested various restrictions like meager solubility, lower bioavailability along with diminished effectiveness because of the blood–brain barrier. Recent developments in nanotechnology present chances to overcome such limitations in targeting. Various nanocarriers have been researched that offer promising targeting capabilities. This review aims to provide an update on various dosage forms based on nanotechnology aimed for AD therapeutics, the patents on nanocarriers for AD and clinical trials on AD drugs.

INTRODUCTION

Alzheimer's disease (AD) is one of the most progressive neurodegenerative disorders in individuals beyond 65 years of age resulting in loss of neurons, and eventually dementia. It is an untreatable disorder with progressive and longer duration (Goedert and Spillantini, 2006) and represents over 80% cases of dementia in the world in elderly individuals. It results in progressive loss of behavioral, mental, functional decline, and other intellectual abilities (Anand *et al*., 2019). Age is the most considerable risk factor; as in 2010, 38% of individuals beyond 85 years of age were troubled with AD which is anticipated to escalate to 51% by 2050 (Herbert *et al*., 2013). Various cardiovascular risk factors, for example, atherogenic dyslipidemia, hypertension, obesity, and diabetes are also associated with AD (Oesterling *et al*., 2014). Because of its constantly expanding rate and societal aging factor, AD has garnered enormous research interest.

Pathophysiology

AD can be distinguished by significant atrophy of the cerebral cortex as well as loss of cortical and subcortical neurons. The neurotic signs of this disorder are senile plaques that are spheric aggregations of the protein beta-amyloid along with declining activities of neurons (also referred to as cerebral amyloid angiopathy) and neurofibrillary tangles (NFTs), consisting of paired helical filaments and other proteins (Braak and Braak, 1994). Neuronal loss as well as pathology might be observed especially in the amygdala, hippocampus, entorhinal cortex and the cortical associated regions of the frontal, temporal, and parietal cortices, and also subcortical nuclei. The tangles deposition occurs in a specific pattern, beginning from the trans-entorhinal cortex; followed by the entorhinal cortex, the CA1 part of the hippocampus and then the cortical associated regions, where frontal, parietal, and temporal lobes are especially influenced. The

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degree and position of tangle arrangement associates well with the seriousness of dementia, significantly more than quantities of amyloid plaques (Kumar *et al*., 2015; Thakur *et al*., 2018).

Advanced AD is characterized by large number of senile plaques and NFTs mostly in the hippocampus and related areas of the cortex, while regions like the visual and motor cortices are moderately spared. This relates to the clinical characteristics of noticeable disability of memory and theoretical thinking, with conservation of vision and movement. Parameters responsible for the particular susceptibility of specific cortical neurons to the pathological outcomes of AD are still unknown (Hardman *et al*., 2006).

The accumulation of tau proteins correlates intimately with intellectual decay and atrophy of brain along with hippocampus. The neuronal pathology of AD involves neuronal loss and temporofrontal cortex atrophy, leading to inflammation, deposition of amyloid plaques, and unusual accumulation of fragments of protein and tangled bundles of filaments. This results in a rise in macrophages and monocytes in the cerebral cortex, and activation of the microglial cells in the parenchyma (Thakur *et al*., 2018). The pathophysiology of AD is exceptionally intricate and relies upon various pathological processes, which have been summed up in Figure 1 and are described in the preceding text.

MANAGEMENT OF AD

The overall management of AD includes pharmacological as well as non-pharmacological treatments. Non-pharmacological approach basically addresses different causes of cognitive impairment and behavioral disturbances. Pharmacological approach, which is described as symptomatic or neuroprotective is based on modulation of disease-related neurotransmitter alterations. At present, approved symptomatic treatment includes cholinesterase inhibitors (ChEIs) and N-methyl-D-aspartate (NMDA) receptor antagonists, (Kumar *et al*., 2015) that depends on their ability to retard the clinical development of symptoms across intellectual, behavioral, and functional areas. Currently approved some of the disease modifying therapeutic drug targets are highlighted in Table 1.

Initially, pharmacological approach for AD was aimed to increase cholinergic transmission in the brain (cholinergic hypothesis). Among the various approaches utilized to raise synaptic levels of acetylcholine (ACh), hindering the disintegration of ACh by acetylcholinesterase (AChE) inhibition was proved to be successful. Inhibition of butyrylcholinesterase (BuChE) enzyme, which is present in lower amounts in normal brain, is present in greater amount in AD brain may also enhance

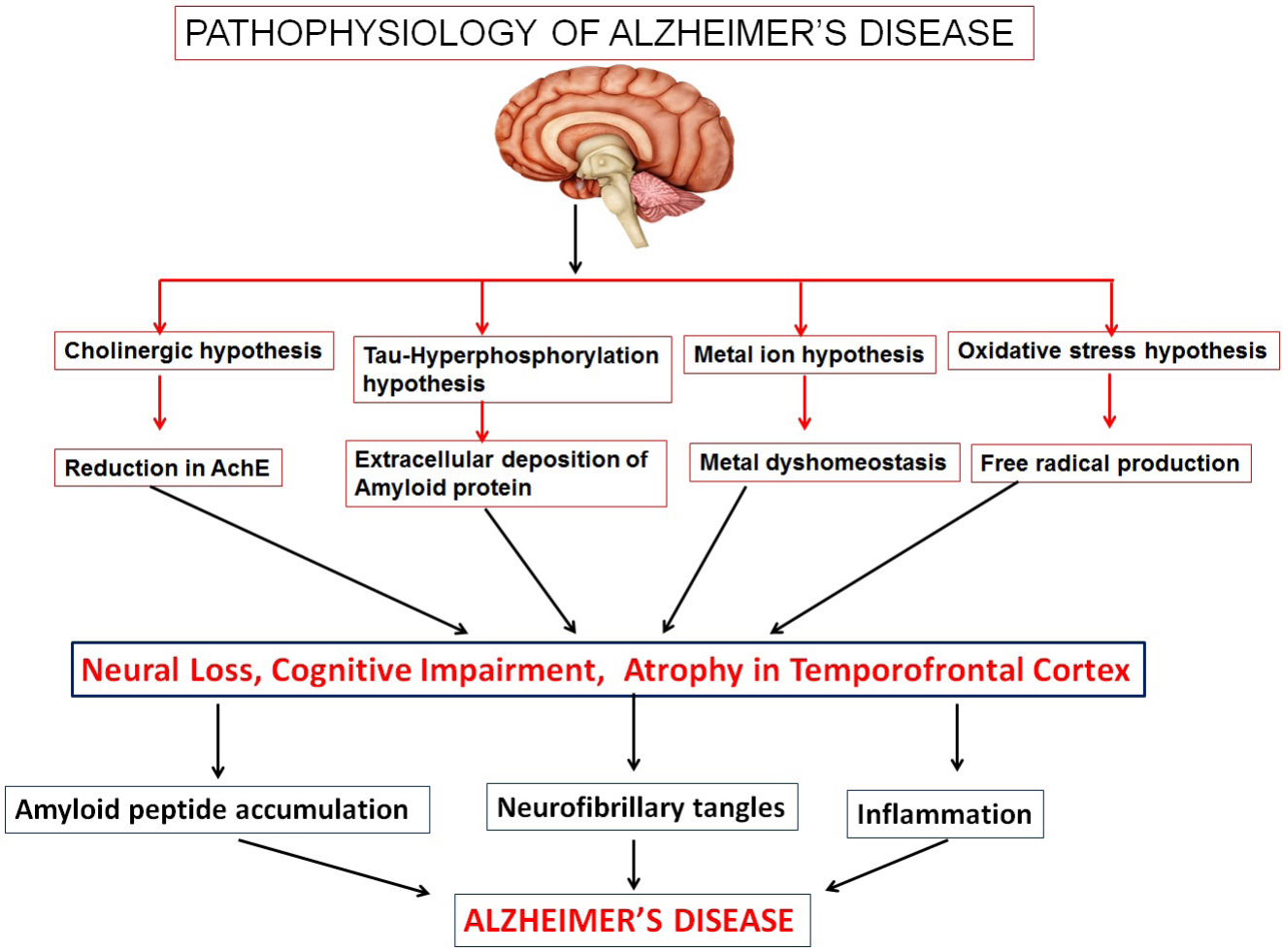

Figure 1. Hypothesis for pathophysiology of Alzheimer's disease.

cholinergic transmission (Thakur *et al*., 2018). Novel approaches of targeting the Aβ and tau-based therapeutics can be significant keys to cater the disease (Anand *et al*., 2014).

Non-pharmacological treatments can enhance the quality of life of individuals with AD (Olazaran *et al*., 2010). A moderate quantity of well-organized randomized controlled trials has evidenced the advantages of different non-pharmacological strategies, such as intellectual training, intellectual rehabilitation, and intellectual stimulation treatment in AD patients (Ballard *et al*., 2011). Various non-pharmacological approaches were reported in Table 1.

The biomarkers manifest significant importance in drug development for AD for choosing the ideal drug candidate for large and high-cost phase-III clinical trials. Biomarkers are also significant in confirming the drug influence on the basic pathophysiology of the disease, which may be required to designate the drug as a disease-modifier (Thakur *et al*., 2018). Generally used biomarkers for AD are compiled in Figure 2.

Table 1. Pharmacological and non-pharmacological therapy for AD.

Pharmacological therapy for AD	
Therapeutic drug targets In AD	**Approach for targeting**
Targeting Aβ protein (anti-amyloid approach)	Targeting amyloid transport
	Modulation of secretase enzymes
	Targeting amyloid aggregation
	Targeting amyloid clearance
	Amyloid based vaccination therapy
Targeting tau protein	Inhibition of tau phosphorylation
	Targeting microtubule stabilization
	Blocking tau oligomerization
	Enhancing tau degradation
	Tau-based vaccination therapy
Targeting intracellular signaling cascades	
Modulating levels of neurotransmitter	Acetylcholinesterase inhibitors (AChEIs)
	Modulation of GABAergic neurons
	NMDA receptor antagonism
	Modulation of serotonin receptor
	Histaminergic modulators
	Modulation of adenosine receptor
Targeting mitochondrial dysfunction	
Targeting oxidative stress	
Anti-inflammatory therapy	
Other pharmacotherapeutic strategies	Cholesterol lowering drugs
	Neuroprotective gonadotropin hormones
	Neurogenesis
	Epigenesis
	Caspase inhibitors
	Modulators of Nitric oxide synthase (NOS)
	Nucleic acid drugs
	Multi-target directed ligands
Non-pharmacological therapy for AD	
Sleep	Music therapy
Physical activity	

POTENTIAL RISK FACTORS ASSOCIATED WITH AD

A few studies have exhibited that hypertension, sedentary lifestyles, and lifestyle-related disorders like type 2 diabetes mellitus and obesity can enhance possibility of AD (Jayaraman and Pike, 2014). Several genetic factors are also responsible for its outbreak and their contribution in its pathogenesis. However, there are no incidences recommending a considerable effect of occupational exposures on AD. Various physiological and other risks associated with AD are encapsulated in Table 2.

APPROVED DRUGS FOR THE TREATMENT OF AD—CURRENT STATUS

ChEIs and NMDA receptor antagonists are the drugs which are used most frequently for the treatment of AD. Donepezil, rivastigmine, galantamine, and memantine are the generally used four FDA-approved drugs; however, combination of donepezil and memantine is also used for AD therapeutics. They improve the quality of life by controlling the intellectual loss and thus motor regulation (Harilal *et al*., 2019). Three of these drugs including donepezil, galantamine, and rivastigmine act on CNS cholinergic pathways. All these have anticholinesterase activity, and galantamine which is a natural-product alkaloid also acts as an allosteric modulator at nicotinic acetylcholine receptors. These drugs are frequently prescribed for individuals in early predementia stage having considerable continuous memory impairment depending on intellectual testing reports (Graham *et al*., 2017). AChE inhibitors may cause g.i. adverse effects such as vomiting and nausea that may be reason for discontinuation of treatment (Santos *et al*., 2015).

Rivastigmine co-inhibits acetylcholinesterase and butyrylcholinesterase and is specific for the G1 rather than G4 form of the enzyme. As compared to other approved drugs, it does not metabolize in liver and, subsequently, does not cause adverse drug reactions of other drugs generally given to elderly individuals with AD. Galantamine shows lower AChE selectivity; vomiting and nausea are its most frequent adverse effects, which are usually self-limiting (Atri, 2019; National Institute for Health and Clinical Excellence, 2011).

In contrast to all other drugs listed above, donepezil has significant effect in AD therapeutics and is given as 5–10 mg tablets once in a day before bed, because of its longer half-life. It selectively inhibits AChE, leading to well response from AD patients with enhancement in intellectual, behavior, and general function. These may be the reason for its more frequent use as compared to other drugs mentioned above (Atri, 2019).

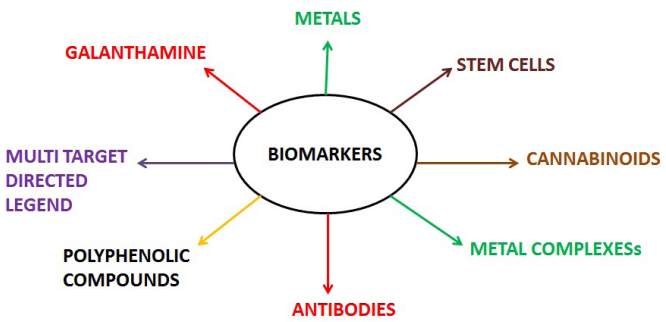

Figure 2. Biomarkers for Alzheimer's disease.

Table 2. Risk factors associated with Alzheimer's disease.

Risk factors associated with Alzheimer's disease	Characteristic features
Obesity	Several reports indicated that obesity during mid-life and underweight during late-life can be the risk factors for dementia and AD may be because of unhealthy regulation of adipokine leading to various health problems e.g. insulin resistance, chronic inflammation, hypertension and hypercholesterolaemia. Hippocampal neurogenesis in adults is also affected by recognized adipokine dysregulation (Atti *et al*., 2008; Beydoun *et al*., 2008).
Hypertension	This factor depends upon the age of the patient, and probably high blood pressure results in increased neuritic plaques and NFTs in the brain causing brain atrophy due to neurodegeneration and hippocampal shrinkage (Hoffman *et al*., 2009).
Physical activity	Although the mechanism is not known, brain activity can be increased and cognitive risks can be reduced by increasing physical activity including yoga and meditation (Gard *et al*., 2014; Streeter *et al*., 2007)
Inflammatory biomarkers	Increased concentration of inflammatory markers in blood like interleukin-6, interleukin-1b, C-reactive protein, lipoprotein-associated phospholipase A2, fibrinogen and alpha-1-antichymotrypsin are reported to cause vascular inflammation and vascular dementia which can be a factor for risk of AD. (Irizarry, 2004; Mrak and Griffin, 2005)
Diabetes mellitus	Diabetes and its complications which are generally responsible for development of vascular diseases play a major role in the pathogenesis along with further development of AD and dementia. Further, elevated insulin resistance also results in hippocampal shrinkage and brain atrophy due to neurodegeneration, again contributing to AD (Breteler, 2000; Stampfer, 2006)
Neurotoxic metals	Metal-based nanoparticles, several pesticides and the most important neurotoxic metals like arsenic, aluminium, mercury, lead and cadmium can alos result in AD because of their capability to raise Aβ peptide and Tau protein phosphorylation, leading to NFTs and senile/amyloid plaques in the brain, indicative of AD (Chin-Chan *et al*., 2015).
Elevated plasma total homocysteine levels	Homocysteine lowers the nitric oxide activity in the brain cells, enhances oxidative pressure and also stimulates the formation of Aβ plaques, which further results in neurotoxicity and neurodegeneration consequently promotes the pathogenesis and advancement of AD (Pacheco-Quinto *et al*., 2006; Selley, 2004).

Table 3. Drugs approved by FDA for treatment of Alzheimer's disease.

Drug (brand Name)	Half-life (h)	tmax (h)	Bioavailability (%)	Protein binding (%)	Type	Stage of AD approved
Rivastigmine (Exelon)	2	0.8–1.7	40	40	Acetylcholinesterase and butyrylcholinesterase inhibitor	Mild to moderate
Galantamine (Razadyne)	5–7	0.5-1.5	85–100	18	Acetylcholinesterase and butyrylcholinesterase inhibitor	Mild to moderate
Donepezil (Aricept)	60–90	3–5	100	96	Selective acetylcholinesterase inhibitor	All stages
Memantine (Namenda)	60–80	3–7	100	45	NMDA Receptor Antagonist	Moderate to severe

Memantine, a recently approved drug for AD, aims to target the NMDA receptors and glutaminergic pathways. Application of memantine in chronic treatment decreases the concentration of Aβ both in aged animals and in AD models. This results in decreased Aβ production. However, in 2005, USFDA refused to extend the application of memantine for mild AD; because of significant adverse effects, e.g. confusion, dizziness, headache, and constipation (Carvalho *et al*., 2015). Riluzole, a glutamate release inhibitor and post synaptic glutamate receptor signaling, is under phase II trial in mild AD patients (Thakur *et al*., 2018).

The combination of memantine and donepezil has also been permitted by USFDA for treating moderate-to-severe AD in individuals who were on 10 mg of donepezil hydrochloride treatment. When memantine is given along with stable cholinesterase inhibitor therapy in patients with AD, a good safety profile was found (Ito *et al*., 2017). Table 3 compiles an overview of pharmacokinetics of drugs used in AD.

DRAWBACKS OF CONVENTIONAL THERAPY

Conventional drug delivery systems including tablet, capsules, powder, or liquid dosage forms have critical restrictions, namely requirement of high-dose, rapid/extensive first pass metabolism, and unfavorable pharmacokinetics leading to low/poor bioavailability (Mudshinge *et al*., 2011). In treatment of AD, drugs administered orally are expected to cross various gastrointestinal barriers, undergo effective absorption, sustain the drug in the systemic circulation, and successfully transport the drug into the blood–brain barrier (BBB), to reach the target site (Stegemann *et al*., 2007). Breakdown of the drug moiety in the gastrointestinal tract accelerates drug elimination, reduces half-life, and reduces bioavailability, thus mitigating the predicted beneficial effects. Additionally, sustained interaction or unpremeditated activation of drug substances at non-specific target sites resulting in several side effects, namely nausea, vomiting, gastric problems, etc. (Sainsbury *et al*., 2014). Few examples are memantine causes dizziness, confusion, constipation, and vomiting (Kornhuber *et al*., 2007). Acetylcholinesterase inhibitors are associated with vomiting and nausea which frequently leads to discontinuance of therapy (Raina *et al*., 2008). Owing to a short half-life of 0.5–3 hours, tacrine needs four administrations in a day (Watkins *et al*., 1994). Furthermore, the physicochemical properties of the drug molecule including the solubility, molecular weight, polarity, partition coefficient, and dissociation constant play an important part in therapeutic effect or drug failure (Alyautdin *et al*., 2014; Sainsbury *et al*., 2014). Furthermore, several bioactive substances like proteins, peptides, and other biological macromolecules have poor solubility and are poorly absorbed in the g.i.t, which is responsible for their lower therapeutic effectiveness and hence clinical trials (Munin and Edwards-Levy, 2011).

NANOCARRIERS IN AD THERAPEUTICS

The primary reasons for frequent therapy failure can be correlated to the adverse pharmacodynamics and

pharmacokinetics of drugs, gastrointestinal instability of drugs, and toxicity (hepato-, neuro-, or renal toxicity) to the tissues (Arias, 2015; Suri *et al*., 2015). Currently approved drugs for AD therapeutics are based on improving neurotransmission or enzyme modulation. The drugs conventionally used to target CNS suffer from the primary constraints of the inability to cross the "BBB" or the "B-CSF barrier" efficiently; and higher drug efflux because of P-glycoprotein activity. Nanotechnology, in conjugation with therapeutics, can be used to control various obstacles faced by drug molecules in the treatment of neurodegenerative diseases. Nanotechnology based dosage forms radically regulate these characteristics of the drug molecules and enhance the therapeutic potential applying various functional aid by utilizing nanotechnology-based dosage forms (Brambilla *et al*., 2011; Nazem and Mansoori, 2008). Nanoformulations not only result in the improvement of pharmacodynamics and pharmacokinetics of drugs, they also have potential to minimize toxicity (Orive *et al*., 2003; Parveen and Sahoo, 2006). Nanoformulations overcome the obstacles by safely carrying the drug through the biological environment with enhanced permeability, thus providing maximum efficiency at a comparatively lower dose. An essential feature of nanoformulations is the controlled drug release at the target site (Safari and Zarnegar, 2014).

Substantial research reports have evidenced the capability of nanoformulations to circumvent oral and intestinal absorption barriers and carry drugs to the site of action (Ensign *et al*., 2012; Lundquist and Artursson, 2016). This is achievable owing to their small size (1–1,000 nm), surface charge, high surface to volume ratio (Singh and Lillard, 2009). In CNS delivery, the BBB barrier presents a great obstacle for the nanoformulations targeting neuronal systems (Misra *et al*., 2003). Altering the surface characteristics of nanformulations enables crossing the BBB by avoiding phagocytic opsonization, thus enhancing the drug levels in the brain (Gidwani and Singh, 2014). The nanosized dosage forms can be classified on the basis of nature of the carrier material as (i) inorganic (gold, carbon, and silica) and (ii) organic (solid-lipid NPs, dendrimers, emulsions, liposomes, and polymers).

Various nanotechnology-based strategies such as polymeric nanocarriers, carbon nanotubes, lipidic nanocarriers, liposomes, nanoemulsions, dendrimers, and metal-based nanocarriers have been evolved over the past decade, focusing on both arresting neurogeneration and neuroprotective for the treatment of AD. Herein, we discuss emerging nanodrug delivery systems for AD therapeutics.

ACROSS THE BLOOD–BRAIN BARRIER

Newly discovered drugs that might be efficacious for the AD treatment may face various hindrances that other drugs used for non-CNS systems may not confront, one of which is the –BBB. The BBB is a highly complex and specialized structure that permits only those substances which are essential for brain activity (Banks, 2012). It is made up of tight junctions in the endothelial membrane that permits just certain molecules to pass through. The tight intersections of BBB are at high transendothelial electrical resistance in comparison to other tissues. There are specialized mechanisms such as specific enzyme systems, protein receptors, and glucose transporters for transporting substances across the BBB. The BBB obstructs undesirable substances from crossing by utilizing tight intersections between cells, extra degradative enzymes, and pumps to eliminate undesirable substances that do pass. Receptors and transporters permit nutrients required for normal functioning to move through to the brain parenchyma (Oesterling *et al*., 2014). The BBB does not have transporters for conventional drugs and so they are generally not able to pass or are actively pumped back out after crossing. This turns into a significant issue for the therapy of neurodegenerative disorders (Edwards, 2001).

Although conventional methods are suitable for treatment of neurodegenerative disorders, they do not have optimum efficacy. This necessitates for the development of therapeutic alternatives for AD. Various approaches can be prodrug formation and the utilization of carrier-mediated transport systems, for example, carbohydrates, peptides, antibodies, gene delivery vectors, nanoparticles, micelles, and liposomes. The mechanisms by which nanocarriers can improve BBB penetration are efflux transport inhibition, nanocarrier cationization, paracellular transport enhancement pharmacologically, or using the hyperosmotic strategy and olfactory delivery of nanocarriers (Shah *et al*., 2013). To cross the BBB, various nanotherapeutic approaches have been adapted (Fig. 3). The approaches include

(i) The affinity and binding of lipophilic nanocarriers for endothelial cells improve the transportation of drug molecule via lipophilic transcellular pathways or endocytosis;

(ii) The adsorptive property of nanocarriers towards blood vessels provided a sustained drug release in the systemic circulation with increased possibility for transport of drug across BBB;

(iii) Additionally, functionalized nanocarriers trigger receptor mediated transcytosis and carrier protein mediated transport of drug candidates across BBB (Saraiva *et al*., 2016).

NANOPARTICLES IN DRUG DELIVERY SYSTEM AND ITS IMPORTANCE

Nanoparticulate drug delivery system is an advanced technology that could be applied to deliver drug substances directly into the brain and has been shown to be extremely efficacious against some CNS disorders. Nanosized systems have garnered considerable interest owing to their favorable features, namely capability to prevent chemical and enzymatic drug degradation, improve drug solubility, and facilitate its transport across the biological membranes. Targeted systems carry the drug straight to the site of action, reduce adverse reactions of the drug, and improve the therapeutic index (Mehmood *et al*., 2015). Various nanoparticulate systems like polymeric nanoparticles, nanoemulsions, liposomes, antibody tethered nanocarriers, dendrimers, etc., are used for drug delivery and some of them are depicted in Figure 4.

While nanoformulations have been investigated for efficacious drug delivery through various routes such as oral, parenteral, topical, vaginal, rectal, etc., they can also play an important part in diagnosis, and imaging. Nanocarriers are also amenable for nasal mucosal vaccination and nasal drug delivery. The nanocarrier systems allow the effective antigen recognition;

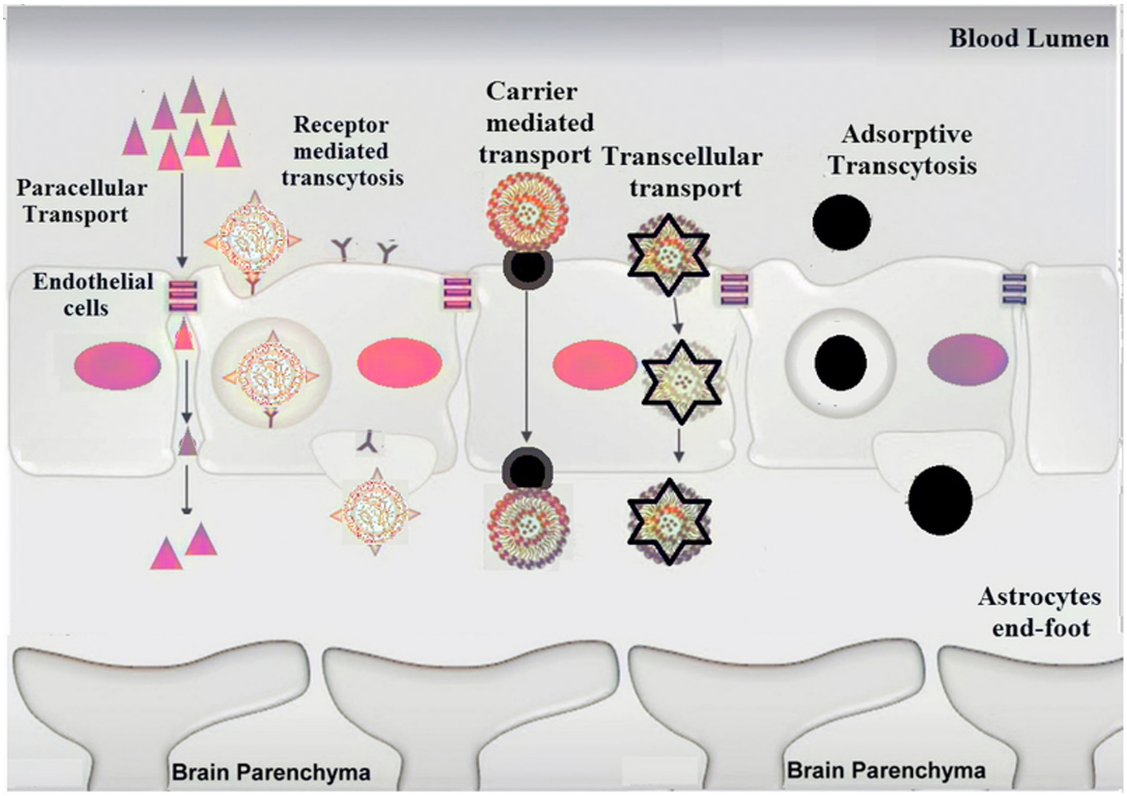

Figure 3. Schematic representation of potential pathways involved in nanocarrier-mediated drug trafficking across BBB associated with AD-nanotherapeutics.

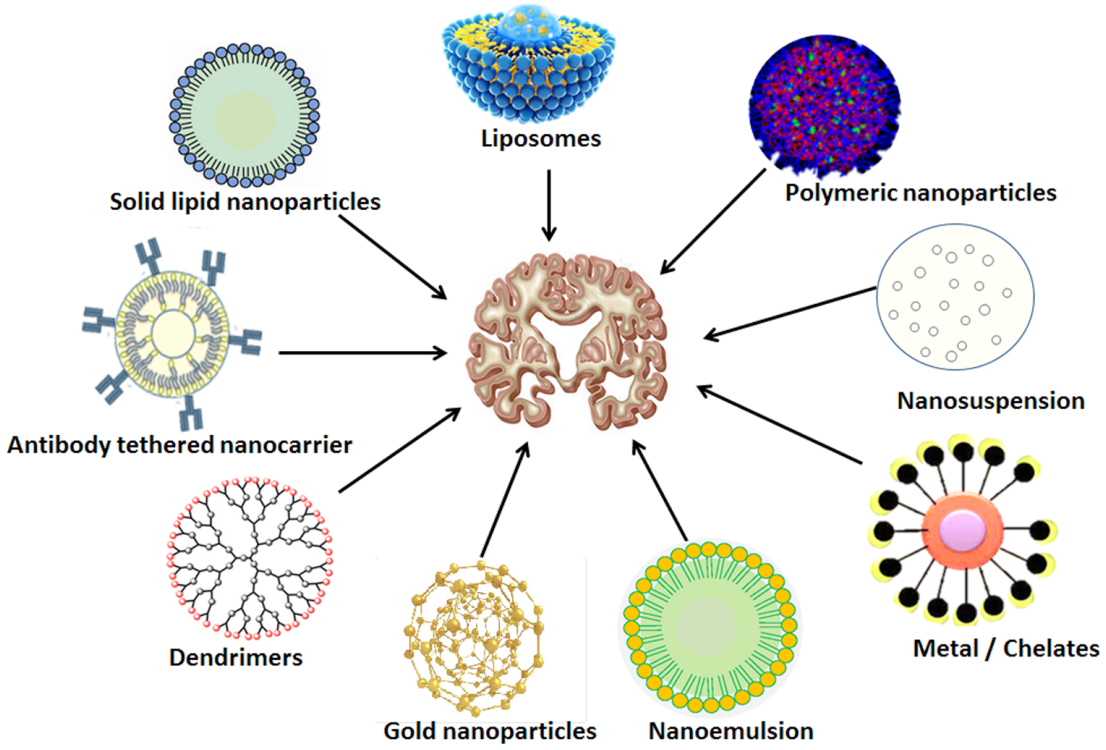

Figure 4. Versatile nanocarriers adopted for mitigation of Alzheimer's disease.

especially nanocarriers based on the lipid and polymer are used for nasal delivery of antigen (Le *et al*., 2019). Nanomedicines played a vital role in the nose to brain delivery. For treating the brain related pathologies, the main focus is on the drug's ability to cross the BBB. The nanoparticulate systems are considered efficient in to achieve brain targeting as they exhibit better penetration of the drugs in the brain. While the need for devices that can allow deposition of the dosage form to the upper part of nose is essential for nose to brain delivery, surface modification of the nanocarrier can act as a strategic approach for perfect nose to brain targeting. Several reports account for targeting of drugs to brain via different nanoparticulates. Of the various nanocarrier systems investigated for brain therapeutics and theranostics in recent years, are either polymeric or lipidic in nature. Polymeric nanoformulations include polymeric nanoparticles, polymeric micelles, and carbon based nanovehicles. Lipidic nanoformulations are liposomes, niosomes, transferosomes, solid lipid nanoparticles, and nanostructured lipid carriers. Nanogels and nanoemulsions have also garnered considerable attention of researchers for transendothelial delivery of neuropharmaceuticals (Oesterling *et al*., 2014).

The BBB is enriched with various transport systems which can transport substances in and out of the brain. The prominent ones are receptor-mediated transport system, transporter-mediated system, adsorptive-mediated transport system, active efflux-mediated transport system, and peptide-mediated transport approach. Mostly, molecules use either of these transport systems to enter and leave the brain with the exception of certain small lipid soluble molecules that cross the BBB transcellularly. These transport systems could serve as efficient routes for the transport of drugs to the brain by improving its permeability (Sweeney *et al*., 2018).

Biological therapeutic agents such as nucleic acids, peptides, proteins, and monoclonal antibodies are being aggressively researched since they have potential to restore the damaged cells and decelerate the progression of AD (Sharma *et al*., 2012). Researchers have developed vaccines for AD and some of them are under clinical trial. Most of the vaccines act on the tau protein in the AD which prevents the functional damage in the brain. Of lately, nano-vaccines (antigen loaded in the nanoparticles as vehicles) have emerged that confer protection to the antigen and result in enhanced efficacy (Wisniewski *et al*., 2016). The drug delivery systems mediated by nanotechnology are primarily based on the brain's transportation of therapeutic agents. Currently the focus is on both specific and non-specific processes for mechanisms to target research of brain locations.

Polymeric nanoparticles

Nanoparticles of 10–1,000 nm can easily cross through various biological and physiological barriers to facilitate rapid transport of drug molecules. The NPs can entrap hydrophilic as well as hydrophobic drugs, and also due to excellent release profile they serve as optimistic drug delivery systems (Kamaly *et al*., 2016). In context to brain delivery, owing to smaller size, NPs can be delivered to cerebellum via olfactory bulb to olfactory cortex and cerebral hemisphere has a caudal pole which carries to the cerebrum. The low efficiency of BBB transportation can be overcome by surface modification of these NPs with antibodies, surfactant, or transferrin (Ghalamfarsa *et al*., 2016).

Muntimadugu *et al*. (2016) investigated encapsulation of the drug tarenflurbil, and recommended for the treatment of AD but failed in the phase III clinical trial due to very low drug permeability in the brain. Tarenflurbil was enclosed in two different nanocarriers, namely solid lipid nanoparticles and poly (lactide-co-glycolic) nanoparticles. A particle dimension of less than 200 nm assured transcellular transport along the olfactory axons (diameter ~ 200 nm) and then paving a direct transport to brain. This was confirmed by pharmacokinetic studies in male Sprague Dawley rats that proved prolonged circulation of the nanoparticles, and the absolute bioavailabilities of intranasally administered poly (lactide-co-glycolytic) nanoparticles was highest followed by solid lipid nanoparticles and drug solution. Similar pattern was recorded for drug targeting efficiency (DTE) and drug transport percentage (DTP). The poly (lactide-co-glycolytic) nanoparticles showed higher DTE (287.24) and DTP (65.18) than solid lipid nanoparticles (% DTE: 183.15 and DTP: 45.41) among all other tested groups. These results confirmed direct transport of tarenflurbil in therapeutic concentration, to brain through olfactory pathway after intranasal administration of lipidic and polymeric NPs.

Elnaggar *et al*. (2015) elaborated intranasal chitosan NPs for targeting piperine into the brain. The oral delivery of neuroprotective piperine suffers due its pre-systemic metabolism and hydrophobicity. The optimized drug loaded chitosan nanoparticles significantly improved the intellectual functions as efficiently as donepezil injection (standard) with additional benefits of dual mechanism (AChE inhibition and antioxidant effect). The nanoparticles alleviated piperine associated nasal irritation, and was devoid of brain toxicity. The authors claimed 20-fold decreases in oral dose of the drug for AD therapeutics.

Likewise rivastigmine, an AChE as well as BuChE enzyme inhibitor, can be given for AD treatment. Nonetheless, the drug has limited entry into the brain because of its hydrophilicity, thus repeated dosing becomes necessary. So, rivastigmine loaded chitosan nanoparticles were prepared by ionic gelation method to improve the uptake of RHT to the brain through intranasal delivery and enhance the bioavailability (Fazil *et al*., 2012). The intranasally administrated drug loaded chitosan NPs generated stronger fluorescent signals in brain as compared to intravenously injected NPs. The brain/blood ratio of rivastigmine for intranasally administered chitosan NPs at 10–480 minutes was 1.35–2.16, higher than that of intranasally administered rivastigmine solution or intravenously injected NPs. The DTE of 355% and DTP of 71.8% suggested better brain targeting efficiency of the developed system.

Amyloid peptides (A beta) (amyloid plaques) are recognized as targets for developing the biomarkers for AD diagnosis. For the sake of developing efficacious in vivo probes, polymeric n-butyl-2-cyanoacrylate (PBCA) NPs were formulated and enclosed with the radiolabeled I125-clioquinol to enhance its delivery to the brain and retention in the amyloid plaque. The nanocarrier was preferentially taken up by AD brain sections compared to cortical control sections. Furthermore, the I125-clioquinol PBCA nanoparticles crossed the BBB in wild type mouse, verifying an increased brain uptake measured in terms of percent injected dose/g compared to I125-clioquinol. I125-clioquinol PBCA nanoparticles demonstrated enhanced brain retention in the

AD transgenic mice against wild type controls. The study exhibited specificity of I125-clioquinol PBCA nanoparticles for A beta plaques both in vitro and in vivo, thus offering a promising delivery vehicle for amyloid imaging (Kulkarni *et al*., 2010).

Lipidic nanoparticles

The nanocarriers, SLNs can also encapsulate both hydrophilic and hydrophobic pharmaceutical drugs (Chen *et al*., 2001). Being in the dimensions ranging from 120 to 200 nm, SLNs are not quickly captured by RES cells and, therefore, are cleared by liver and spleen filtration. Moreover, by adding a specific ligand on their surface, their drug-targeting ability can be improved. In fact, many pharmaceutical molecules, other than those intended for AD therapeutics, have been delivered to the brain via receptor-mediated transcytosis mechanism (Grumezescu AM *et al*., 2016; Mozafari M, 2020).

These lipidic systems are efficient nanocarriers that can competently upload versatile therapeutics and bioactive agents. The system quite resembles with lipid emulsion, liposomes, and polymeric nanoparticles. Literature envisaged that SLNs behave as low-density lipoproteins, and, therefore, get interacted with LDL receptors present on blood–brain barrier (Ghasemiyeh and Mohammadi-Samani, 2018). The created network of SLNs and receptors let entry of SLNs inside BBB (Fig. 5).

These formulations are feasible to fabricate without use of organic solvents, are cost effective, have reproducibility, and offer several advantages over other nanocarriers, i.e., controlled release (for weeks), site specific drug delivery (neurons, cancer cells), stability (~ 3 years), etc. Nanoscaled size range (50–200 nm) enables these particles to circumvent liver/spleen filtration, assists to escape from RES (reticuloendothelial system), and facilitates to cross tight junctions of BBB (Mukherjee *et al*., 2009). Table 4 summarizes few research reports on SLNs for AD targeting.

Magnetic nanoparticles

In the recent years, magnetic NPs have been extensively explored and are applied for both diagnosis and therapeutic reasons. Their inert nature associated with low toxicity suggests implications in brain pathologies including AD. Kong *et al*. (2012) in an experiment in a mouse model suggested that magnetic NPs can permeate the normal BBB when an external magnetic field is applied. On systemic administration, an applied strategic external magnetic field navigates the magnetic nanoparticles to cross the BBB and aggregate in a perivascular zone of the brain parenchyma. Internalization by endothelial cells was suggestive of transcellular trafficking as the BBB crossing mechanism. Furthermore, remote radio frequency magnetic field can be utilized to release drug from silica coated magnetic nanocapsules. In conjunction, the results

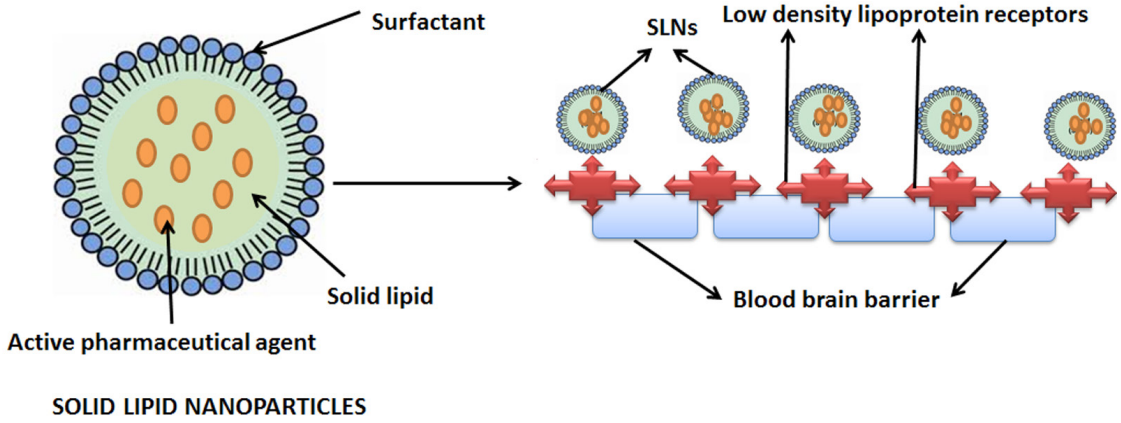

Figure 5. Schematic illustration of composition of SLN and its interaction with LDL receptors.

Table 4. SLNs for the treatment of AD.

SLN approach	Research outcome	Reference
Resveratrol SLN functionalized with antitransferrtin receptor monoclonal antibody for inravenous administration	Developed antibody conjugated SLNs to be taken up through brain endothelial cells. They were able to cross BBB, hence have attribute for the treatment of AD.	Loureiro *et al*., 2017
Transferrin modified quercetin SLNs for neuroprotective activity	Developed SLNs for ease of passage across BBB via transferrin receptor available on brain cells. A experimental study revealed suppression of amyloid peptide aggregation and fibril formation by developed transferrin functionalized quercetin SLNs.	Pinheiro *et al*., 2020
Erythropoeitin loaded SLNs for better BBB permeation and neuroprotective efficacy	Morris water maze test on rats investigated improved restoration of cognitive cells in AD affected rats. Prepared erythropoeitin-SLNs diminished oxidative stress and plaque deposition in hippocampus region.	Dara *et al*., 2019
Phosphotidylserin functionalized nicotinamide loaded SLNs for	Intraperitonially administered phosphotidylserin-nicotinamide SLNs exhibited augmented cognitive neuronal activity, preserved memory cells and reduced deposition of tau hyperphosphorylation in AD affected rat model.	Vakilinezhad *et al*., 2018
Piperine loaded SLNs for reduction in oxidative stress and cholinergic degradation in brain cells	Piperine SLNs were coated with polysorbate 80 for brain specific targeting. Histopathological study exhibited reduction in plaque and tangle phenomenon in 2 mg/kg dose equivalent.	Yusuf *et al*., 2012

suggest a meticulous approach for manipulating the biodistribution of MNPs in the brain via an external magnetic field.

In a strategic approach, an electromagnetic actuator was designed for guiding magnetite containing drugs (Do *et al*., 2016). These magnetic nanoparticles were capable to cross BBB after applying external electromagnetic fields [28 mT (0.43 T/m)]. Additionally, the brain uptake and transport rates of magnetic nanoparticles were considerably improved by applying a pulsed magnetic field. The localization of NPs monitored using fluorescent magnetic nanoparticles demonstrated the feasibility of the magnetic nanocontainers as valuable targeting system for AD diagnosis and therapy.

Nanoparticle conjugates

Functionally integrating proteins, peptides, antibody, DNA, and other nucleic acids with NPs have developed a large variety of composite nanomaterials which in many cases, display augmented properties because of synergistic effect of both components. These capabilities are drawing increased attentiveness from researchers searching of new nanosize options for diverse applications that include therapeutics, cellular delivery, and diagnostics (Jeong *et al*., 2018). Table 5 compiles few promising approaches containing nanoconjugates to combat neurological disorders.

Xiong *et al*. (2017) developed peptide-gold NPs comprising two inhibitory peptide sequences (VVIA and LPFFD) for amyloid-β aggregation. The system was targeted to inhibit accumulation of Aβ proteins. The two peptide sequences were conjugated onto the gold NP surfaces and ordered/oriented in optimal conformation to effectively inhibit amyloid-β protein accumulation. Using the two different peptides on a single NP was greatly synergistic, prohibiting amyloid-β proteins accumulation more strongly with less cytotoxicity, compared to the free peptides.

AD is distinguished by the cerebral aggregation of extracellular amyloid plaques and can target on a dual-functional nanoparticle (TQNP) to deliver biotechnological drugs, namely the H102 peptide, a β-sheet breaker, to AD lesions precisely. A spherical, dual-function, drug delivery system loaded with H102 (TQNP/H102) was designed by Zheng *et al*. (2017). Two targeting peptides, TGN and QSH, were linked to the surfaces of NPs to allow BBB transport and Ab42 targeting, respectively. The study revealed that TQNP could be taken up via various routes, including caveolae-mediated endocytosis, indicating that some of TQNP could cross the BBB intact.

A hybrid system for amyloid plaques targeting siRNA delivery was developed using PEGylated Poly (2-(N, N-dimethylamino) ethyl methacrylate) (PEG-PDMAEMA) joined with two d-peptides, a CGN for brain penetration, and a QSH for β-amyloid binding. The hybrid complex composed of 25% QSH-PEG-PDMAEMA, 50% CGN-PEG-PDMAEMA, and 25% MPEG-PDMAEMA encapsulating siRNA showed negligible cytotoxicity and conferred protection to siRNA from enzymatic degradation. It was determined that the complex was taken up by neuron cells suggesting that the complex was capable of escaping from lysosomes, releasing siRNA in the cytoplasm, and, therefore, establishing effective gene silence (down-regulated protein level to 18.5%). Post i.v. injection, the intact hybrid complex penetrated into the brain and was localized around the amyloid plaques in transgenic AD mice. The precise delivery leads to increased therapeutic activities, which was affirmed by the poor yield of enzyme-digested products sAPPβ (−42.6%), the strong mRNA (36.4%) knockdown of BACE1 (a therapeutic target of AD), as well as the better neuronal protection than the single component complexes. The results are suggestive of an efficient and precise nanocarrier for delivery of siRNA to the AD lesion that may be future candidate for gene therapy for AD (Zheng *et al*., 2017).

Cubosomes

These are liquid crystalline nanostructured particles consisting of biocompatible carriers. A cubosome is comprised of a three dimensionally organized bicontinuous curved lipid bilayer separated by two aqueous channels within which the bioactive ingredients and proteins come into contact (Fig. 6) Their distinguishing characteristics are that they can encapsulate

Table 5. Research highlights of few nano-conjugates developed for treatment of Alzheimer's disease.

Strategy	Research highlights	Reference
Intranasal delivery of nanoparticles conjugated with *S. tuberosum* lectin (STL) modified basic fibroblast growth factor by the virtue of selective binding of STL to nasal epithelial N-glucosamine.	The developed intranasal system exhibited approximately five times greater drug distribution at the affected area of brain comparable to injectable NPs.	Zhang *et al*., 2014
Surface modified positive allosteric modulaters (PAM)	The developed system enhanced binding affinity of Ach to the muscarinic receptors thus improves bioavailability in brain. The prepared conjugate reported better efficacy at low dose when co-administered with AChE inhibitors	Kumar *et al*., 2017
Nanoconjugate of tacrine with 1,2,4-thiadiazole derivatives	Prepared tacrine conjugates were stable and showed greater BBB permeability. They have potential for inhibition of butylcholinesterase enzyme (BCHE). These conjugates were free radicle scavengers that checked amyloid deposition in brain.	Makhaeva *et al*., 2020
Impressive regimen containing chitosan-based simvastatin-citicolin conjugate nanoparticles (~ 300 nm) with minimum undesirable side effects.	Co-administered simvastatin and citicolin therapeutics from the chitosan conjugate system proved effective tool for the management of Alzheimer's disease with lessened side effects.	Mozafar *et al*., 2020
Multifaceted 3-phenylcoumarin lipoic acid conjugate for treatment of Alzheimer's disease	Developed conjugates were evaluated for neuroprotective activity against H_2O_2 induced cell death. The system displayed potent AchE inhibition, antioxidant and metal chelating activity.	Jalili- Baleh *et al*., 2018
Dihydrolipoic acid(DHLA)/ CdSe-ZnS/ Amyloid beta conjugated QDs for inhibition of Aβ-fibrillation	Nanoscaled DHLA capped conjuagated QDs of approximately 2.5nm were prepared that contained CdSe/ZnS conjuage. The system aimed to reduce amyloid fibrillation process in brain tissues. This QD conjugate adhered over Amyloid peptide in aqueous phase. Significant fibril morphology alteration and lessening in fibrillation process were observed.	Thakur *et al*., 2011

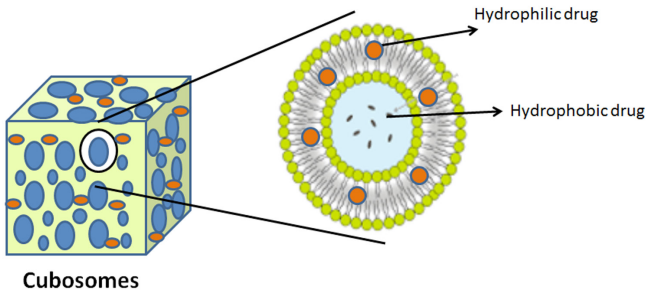

Figure 6. Composition of cubosome drug delivery system.

substances that are hydrophobic, hydrophilic, and amphiphilic, maintain controlled release of the drug and bioadhesion, are thermodynamically stable, and are promising vehicles for various drug administration routes (Karami and Hamidi, 2016).

Wu *et al*. (2012) developed lectin modified non-immunogenic odorranalectin (small peptide) cubosomes. The system was conjugated with streptavidin through incorporating maleimide PEG oleate and aimed for effective nose to brain drug delivery. The relative uptake of odorranalectin cubosomes was 3.46 times higher compared to the bare cubosomes in brain tissues. Pharmacodynamic study on rats after intranasal administration revealed enhanced efficacy of streptavidin conjugated odorranalectin cubosomes for the mitigation of Alzheimer's disorder that suggested a potential non-invasive peptide and protein delivery approach in brain tissues.

Piperine, a memory enhancing natural alkaloid, was used for developing novel oral cubosomal delivery system by Elnaggar *et al*. (2015) for the treatment of neurological AD. Various bioactive surfactants (Tween, cremophore, and poloxamer) modified crystalline cubosomes were evaluated for pharmacokinetic and pharmacodynamics assessments. Among them, Tween 80 modified piperine cubosomes exhibited effective anti-apoptosis and prominent anti-inflammatory activity performed through Caspase-3 assay. Nanoscaled dimension (~167 nm), low polydispersity index (0.18), and optimum zeta potential of developed cubosomes exhibited high entrapment efficiency (~88.7%) and superior stability. Developed novel oral cubosomes depicted potential for inhibition of AD progression.

Inorganic nanoparticles

Gold and silica nanoparticles are designated for the impressive management of AD owing to their exclusive transcytosis movement through endothelial cells of brain without surface modification. These positive charged nanoparticles are self-sufficient for the carriage of bioactive agents across targeted brain tissues. A lot of inorganic NPs are reported that successfully crossed BBB, designed for nose to brain delivery without surface modifications. Intranasal silicon coated NPs (mean particle size 200 nm) were developed for effective brain targeting (Masserini, 2013).

PEG coated iron oxide NPs were demonstrated by Wadghiri *et al*. (2013) for improved BBB permeation. Although inorganic nanoparticles are highly concerned with immunotoxicity, inorganic NPs (silicon oxide) have been extensively explored for brain targeting owing to their biocompatibility and minimal cytotoxicity. In this context, silicon quantum dots (QDs) are widely explored as theranostic system that serves both as therapeutic and diagnostic agent for the management of neurological diseases. QDs proficiently cater drug delivery at the target sites, monitor cellular uptake with less cytotoxicity. Moreover, the fluorescent silicon QDs have been utilized for cellular imaging and diagnosis of the neuronal diseases (Sivasankarapillai *et al*., 2019).

Silica nanoparticles (SiNPs) were designed as novel drug delivery systems for BBB targeting due to their profound cellular uptake efficiency and localization in the cytoplasm. These NPs were significantly deposited in the intracellular amyloid cells (Aβ1-42), thus facilitating alleviation of AD (Yang *et al*., 2014). Developed SiNPs have potential to reduce cellular apoptosis and reactive oxygen in the intracellular region in dose dependent manner. Amyloid peptide deposition and increased tau phosphorylation are the two distinct pathological hallmarks of AD. Both were notified for the activity of silica nanoparticles to check their efficiency for diminishing Aβ (1–42) plaque formation and hyperphosphorylation. However, cellular uptake study performed in mouse neuroblastoma cells and human brain model (SK-N-SH) revealed neurotoxicity after administration of 10 µg/ml SiNPs for 24 hours. The developed system got deposited in the cytoplasm, reduced cell viability, and increased pathogenesis of AD.

Gold nanoparticles (Au NPs) have been extensively used to mitigate neurological disorders owing to their efficiency to cross BBB that project important role in retrieval of depreciated behavioral aspects of brain cells in AD. Developed AuNPs significantly suppressed amyloidosis, checked aggregation of oligomers, and avoided fibril formation within 72 hours (Chiang *et al*., 2020). Sanati *et al*. (2019) worked for the development of Au NPs and investigated their impact on memory cells. The outcomes revealed improvement in acquisition and retention in AD. The study was conducted in rat animal model (Morris water maze) to investigate restoration of memory cells after intraperitoneal and intrahippocampal injections of developed AuNPs. The results showed reduction in retention time of memory and spatial learning cells by AuNPs in rats, i.e., ~25.7 seconds compared to non-treated memory cells (39.6 seconds). Moreover, other brain derived factors such as Brain-derived neurotrophic factor (BDNF), cAMP response element binding protein (CREB), and neural survival rates were also modified interpreting improved neural behavior. The developed system displayed promising efficiency for AD outbreak.

Antibody-tethered nanoparticles

Of lately, researchers from University of Cambridge have disclosed a methodology that demonstrates designing of an antibody that can recognize and quantify toxic particles (amyloid beta oligomers) associated with destruction of human healthy brain tissues/cells. Antibodies are proteinaceous molecules that identify and neutralize pathogens/microbes by the virtue of their affinity towards oligomers (Fig. 7). This innovation in healthcare sector would pave of management strategy against the AD (Francesco *et al*., 2020).

Antibody conjugated novel delivery approach is considered as promising clinical strategy for mitigation of AD. These antibody tethered systems reduce amyloid protein/plaque deposition at the presynaptic phase of the neurological disorder and hence facilitate retrieval of diminished memory cells of brain.

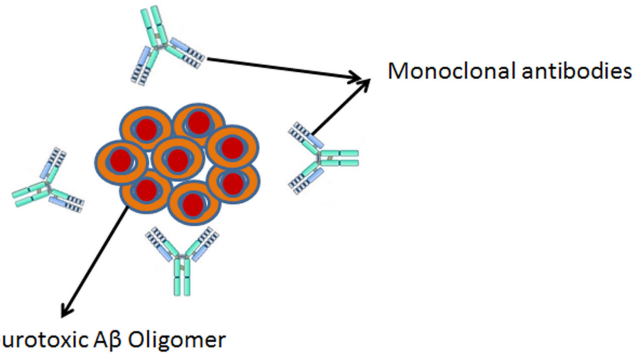

Figure 7. Monoclonal antibody-oligomer interaction to neutralize amyloid plaque.

In this context, monoclonal antibodies (MAb) have displayed satisfactory capability to target amyloid β peptides in AD affected transgenic mice and human brain tissues. Numerous MAbs, i.e., solanezumab, bapineuzumab, and crenezumab have been explored for the evolution of brain drug delivery systems (Watt *et al*., 2014).

MAbs sweep away undesirable amyloid protein either by passive immunization or through complement activation and check neurodegeneration process. Although, solanezumab and bapinezumab were reported to non-specifically target the amyloid protein and delayed the AD treatment time comparative to crenezumab monoclonal antibody (Prins *et al*., 2015).

Rosse (2017) presented a series of conjugates composed of antibody-drug to combat wide range of inflammatory diseases, namely, AD, atherosclerosis, Parkinson's disease, rheumatoid arthritis, etc. These conjugates were fabricated through phosphate-based linkers associating immunoglobulin proteins (CD74/CD163) and therapeutics as steroids (Rosse, 2017).

Another, antibody tethered PBD-C06 formulation (anti-pGlu3-Aβantibody) has been developed through grafting murine antigens on light and heavy chains of antibody. This immunotherapeutic approach was designed to target pGlu3-Aβepitope to mitigate the pathology of AD. Developed PBD-C06 has affinity for oligomers, monomers, fibrils, and clustered Aβpeptide that efficiently targeted neurotoxic peptides at site. Significant reduction of inflammation in the intracellular cells was reported that suggested potential clinical application in vasogenic edema (Hettman *et al*., 2020).

Nanocomposites

In AD, most of the therapy and therapeutics are focused on amyloid Aβ peptide as it hinders functions of memory cells and causes dementia. In this perspective, tau pathway is extensively correlated with AD symptoms, pathology, and clinical development.

Methylene blue, an inhibitor of tau aggregation, was loaded on CeNC-IONC-MSN-T807 to make nanocomposite. Developed system exhibited profound affinity towards tau and checks AD pathogenesis. Moreover, the designed system depicted symptomatic relief through hindering process of hyperphosphorylation and alleviating mitochondrial oxidative stress. A significant reduction in neuronal cells was observed that rescued destruction of memory cells in AD affected rats (Chen *et al*., 2018).

Karaboga *et al*. (2020) developed nanocomposite biosensor comprising of reduced graphene oxide and gold nanoparticles. The surface of nanocomposite was functionalized with 11-mercaptoundeconoic acid to target tau-441 protein accountable for degeneration of memory cells. Developed functionalized nanocomposite has potential to capture tau-441 proteins at a concentration 0.091 pg/ml that offered targeting proteins present in serum and cerebrospinal fluid.

Quercetin, a flavonoid is reported to inhibit Aβ plaque deposition owing to its antioxidant property. However, poor water solubility and extensive first pass metabolism restrict the usage of quercetin in the management of neurological disorders. Selenium nanocomposite containing quercetin and sodium selenite was synthesized and modified with polysorbate 80. The developed template possessed high aqueous solubility and capacity to cross BBB efficiently in comparison to plain quercetin. The outcomes suggested improved inhibition of Aβ fibrillation and antioxidant activity (Qi *et al*., 2020).

Zhao *et al*. (2019) demonstrated novel synthesis of nanocomposites to eliminate Aβ induced neurotoxicity in AD affected mice. Nanodimensional clusters containing cross linked KLVFF proteinaceous body were developed through in situ polymerization. The prepared bioactive system altered the morphology of amyloid peptide aggregates and reduced the population of pathological oligomers at the infected site. The nanocarriers system lessened neuronal injuries caused by amyloid aggregation and plaque deposition. Thus, nanoscaled composites presented feasible approach for protection of AD affected hippocampal neurons and enabled fast recovery of endocranial microglia efficiency (Zhao Y).

Nanoemulsions

Thermodynamically stable nanosized emulsions have been explored for effective import of bioactive agents across BBB owing to their advanced pharmaceutical designing. Innovative surfactants and co-surfactants enable nanoemulsion as potential drug delivery approach for the management of neuronic disorders. Their small particle size (50–500 nm) let uniform dispersion and higher payload of therapeutics for the site specific delivery.

Memantine embedded nanoemulsion has been reported for impressive intranasal drug delivery. This approach bypassed BBB and was found to be effective for AD therapeutics. Formulated nanoemulsion depicted mean globular size of approximately 11 nm, with 80% drug release in simulated nasal fluid. On intranasal administration, memantine loaded nanoemulsion exhibited amplified antioxidant efficiency and superior cellular uptake in brain cells of experimental rats (Kaur *et al*., 2020a). The oil in water donepezil hydrochloride loaded nanoemulsion was prepared utilizing 10% each of labrasol and glycerol. Nanoscaled, uniform, and stable particles of nanoemulsion impacted the AD infected brain cells. Cytotoxicity behavior investigated on Sprague Dawley rats through nasal route revealed dose dependent efficacy without disturbing the morphology of cells. The antioxidant and radical scavenging efficacy revealed promising potential of donepezil hydrochloride nanoemulsion for treating neurological diseases. Outcomes of scintigram defined maximum cellular uptake by brain cells (Kaur *et al*., 2020b).

Recently, selective AChE inhibitor, Huperzina A, was explored for nose to brain delivery to mitigate AD. Extensive researches on conventional dosage of Huperzina A demonstrated its noticeable adverse effects in the peripheral cholinergic region and gastrointestinal tract. Huperzina A nanoemulsion modified with lactoferrin (Lf-HupA-NE) was investigated against in vitro brain model (Hcmec/D3 cells). Lactoferrin, an iron binding glycoprotein, is widely expressed in brain endothelial cells and highly utilized in the treatment of age related neurodisorders. Thus developed nanoemulsion on intranasal administration was targeted to brain cells and tissues. The results notified impressive drug release in the brain parenchyma and suggested brain targeted drug delivery systems (Jiang *et al*., 2019).

Md *et al*. (2018) revealed neuroprotective property of naringenin bioflavonoid. Its restricted permeation coefficient across biological membrane limits its pharmaceutical applications. Naringenin loaded nanoemulsion was investigated against amyloid peptide induced toxicity in the brain cells (SH-SY5Y). The outcomes defined alleviation of amyloid induced reactive oxygen species and exhibited neuroprotective action in SH-SY5Y neuroblastoma cells in the brain. Designed nanoemulsion depicted promising approach for reducing phosphorylated tau level and amyloidogenesis related to AD.

Liposomes

Liposomes are self-aggregating lipid nanosystems that amalgamate and supply the CNS with lipophilic drugs, hydrophilic drugs, protein-based drugs, and nucleic acid components (Pashirova *et al*., 2018). The lipophilic characteristics of liposomes assist the transportation of drugs across the endothelial membrane of brain cells and provide them with outstanding brain uptake characteristics. Drug diffusion and liposome endocytosis are the two prominent mechanisms engaged in drug release from liposomes (Wei *et al*., 2014). Although, vesicle size and lipid composition do affect their transmission in the systemic circulation and in cellular uptake in brain cells (Montesinos, 2017). Liposomes offer high pay loads both for hydrophilic and hydrophobic therapeutics (Fig. 8).

Research on liposomes demonstrates its versatile pharmacological actions, i.e., neuroprotective, anti-ischemic, anti-epileptics, and antimicrobials. These formulations have been explored as cargo for import of therapeutics across BBB through active targeting. Austen *et al*. (2008) carried out a study based on inhibition of Aβ aggregation and toxins in the fibrils on brain cells. They developed stable retro-inverso peptides capable to crossing BBB. The system was modified with fluorescein labeled inversion to amplified anti-amyloid aggregation property. In vivo study on transgenic mice (TG2576) after peripheral injection revealed protection of memory cells of brain.

Behl *et al*. (1994) formulated curcumin loaded liposomes for the impressive management of AD. Antioxidative curcumin liposomes offered anti-amyloid effects. The outcomes demonstrated neuroprotective efficacy against amyloid toxins released in brain endothelial region. Adorned phenolic group in curcumin therapeutic got bound with amyloid proteins, diminished plaque deposition, and facilitated aggregation free environment around brain cells.

Arumugam *et al*. (2008) demonstrated treatment of AD through rivastigmine loaded liposomes administered intranasally. The delivery system sustained the drug release effect that could reduce frequency of drug administration and ultimately patient compliance. Augmented half-life and higher concentration of rivastigmine in brain cells were reported after oral and intranasal administration.

Zheng *et al*. (2015) encapsulated H102, a novel peptide (βsheet breaker) in liposomes to avoid degradation and enhance brain penetration through intranasal drug delivery for AD therapeutics. The formulated liposomes had ability to penetrate Calu-3 cell monolayers consistently. After drug administration through nasal route, H102 was effectively delivered to the brain and produced the three times greater effect in the brain. The delivery produced excellent spatial memory. The liposomal intranasal brain delivery approach for H102 was stable, effective, and safe.

Donepezil encounters hurdles in crossing BBB, hence is not preferred in conventional dosage formulations. To avoid this problem, donepezil was loaded in liposomes and intranasally administered which reduced the risk of first-pass metabolism, unwanted side effects, and persisted rapid drug delivery to the CNS. Pharmacokinetic study of both donepezil loaded liposomes and free donepezil administered through oral and intranasal routes revealed improved bioavailability of the former owing to its better absorption via intranasal administration. A twofold increase in the AUC of donepezil liposomes administered intranasally was observed compared to oral route. Microphotographs of brain and olfactory bulb revealed no morphological changes in the visceral tissues after intranasal administration of liposomes after intranasal administration in rats. Donepezil loaded liposomes given through intranasal route showed improved bioavailability in brain, enhanced cellular uptake, and reduced cellular toxicity (Al-Asmari *et al*., 2016).

Dendrimers

The three dimensional, spherical, branched architectural entities (dendrimers) are emerging pharmaceutical nanocarriers,

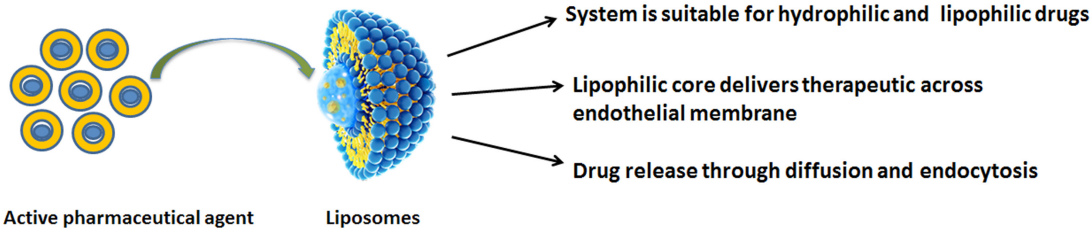

Figure 8. Nanocarrier: liposomes and its salient features.

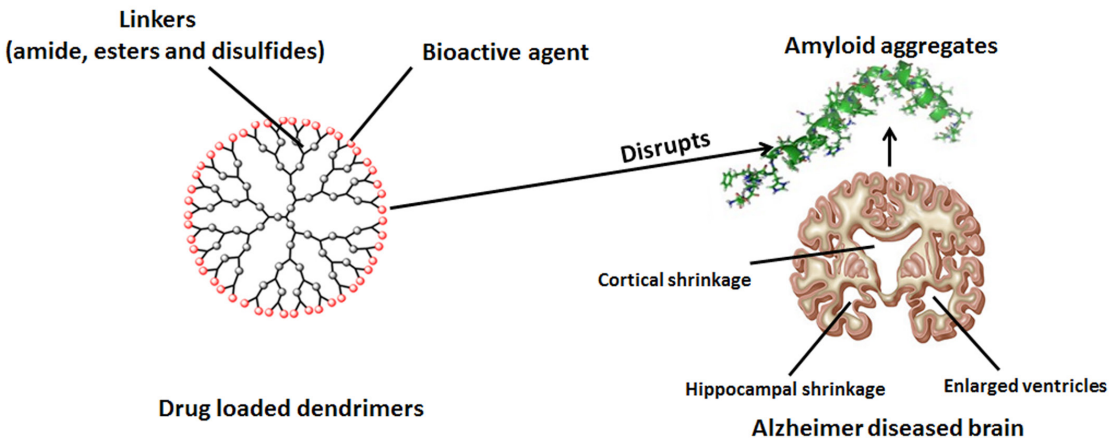

Figure 9. Drug loaded dendrimers for treatment of AD.

widely worked out for designing numerous targeted drug delivery system owing to their versatile properties, i.e., nanosize, low polydispersity index, high payload efficiency, improved solubility, less viscosity, biocompatibility, non-immunogenicity, and stability. The morphology of dendrimers is comprised of functional groups containing linkers attached with therapeutic agents on their periphery (Fig. 9). Their specific structure facilitates site specific drug delivery. For the effective treatment of neurogenerative disorders, extensive research and formulations based on dendrimers are reported. Presence of multiple functional groups or polyvalent recognition sites enable high pay load of therapeutics (Abbasi *et al*., 2014).

In AD, several molecular mechanisms are involved such as apoptosis, inflammation, and oxidative stress. These processes should be targeted through designing nanoengineered dendrimers. Numerous bioactive agents, i.e. peptides/protein, nucleic acids, genes, and biosensors are frequently loaded in dendrimers for brain delivery (Aliev *et al*., 2019).

Katare *et al*. (2015) stated that drug delivery to the brain is challenging because of the low aqueous solubility and bioavailability. The haloperidol dendrimer was delivered to the brain through the nasal route of administration. The developed preparation showed hundred times high aqueous solubility. Cataleptic and locomotor studies were evaluated after intraperitoneal injection administration of haloperidol dendrimers. Haloperidol response given through nasal and intraperitoneal route was compared. It was mentioned that 6.7 times less dose was required for nasal delivery to obtain same behavioral response compared to intraperitoneal route. The study suggested improvement in aqueous solubility of poorly soluble drug through dendrimers for the amplified locomotors action in AD cases. The study confirmed that the dendrimers given via nasal route is suitable delivery for targeting brain for poorly aqueous soluble drugs.

Nazem and Mansoori (2011) described various biomedical applications of dendrimers due to their shape and size. The anti-myeloid strategy was recommended for the dendrimers. The strategy was designed in such a way that the peptide monomer was attached to the end of fibrils which resulted in the prevention of cytotoxic effects. The most frequently researched dendrimers for the therapy of brain diseases are polyamidoamine (PAMAM) dendrimers. The effect of PAMAM dendrimers on prion peptide PrP185-208 and Alzheimer's peptide Aβ1-28 was assessed using thioflavin T dye. Outcomes of the fluorescence and electron microscopy revealed high degree of amyloid aggregation and signs of fibril disruption. The interaction of globular and branched dendrimers with amyloid proteins showed inhibition of fibril formation in AD (Klajnert *et al*., 2006).

Another anti-inflammatory and antioxidant therapeutic N-acetyl-l-cysteine was explored for the synthesis of poly (amidoamine) (PAMAM) dendrimers. The synthesized system was capable of intracellular drug delivery at the site of inflammation. Presence of detachable disulfide bonds in the integrity of dendrimers enabled linking with intracellular glutathione and microglial cells. Higher payload facilitated desirable amount of drug release at local cells and exhibited improved antioxidant activity (Navath *et al*., 2006).

Klementieva (2019) discussed exclusive brain cell protective activity of poly propyl imine (PPI) dendrimers functionalized with maltose in transgenic mice. PPI dendrimers modified with maltose got bound with amyloid proteins, hindered their aggregation and checked fibril deposition at brain cells. The study revealed that unmodified PPI dendrimers cause cellular toxicity, whereas maltose modified dendrimers did not show intrinsic toxicity. The research highlighted that polysaccharide coated dendrimers were non-toxic to the neuroblastoma cells. Dendrimers containing cationic PAMAM and phosphorous have been fabricated through polymerization technique to investigate efficacy against deposited amyloid peptides over neuroblastoma cells. The intrinsic toxicity due to positive charge of PAMAM restricted the performance of dendrimers. Biocompatible sugar coated glycodendrimers have also been reported. The modified dendrimers were capable of interacting with amyloid proteins with minimum cell toxicity. The developed sugar coated glycodendrimers were taken account for symptomatic relief in AD owing to their high surface group density over protofibrils G4 of brain cells (Benseny-Cases *et al*., 2012).

Nanosuspensions

Pharmaceutical nanoscaled biphasic suspensions are acceptable drug delivery systems for hydrophobic drug

therapeutics owing to their stable and well dispersed appearance. Availability of a series of natural/synthetic surfactants and the ease of preparation methodologies enable nanosuspensions for targeted drug delivery through oral, parenteral, pulmonary, ocular, and topical routes (Yadollahi *et al*., 2015).

Donepezil nanosuspensions prepared through ionic crosslinking method with chitosan were investigated in Sprague Dawley rats for olfactory pathway following nose to brain administration. Fine nanoscaled particles (mean size 200 nm) and low polydispersity index (0.341) provided better absorbance and bioavailability in brain. The animal study revealed effective donepezil responses to the brain cells (C_{max} 7.2 ng/ml) and plasma (82.2 ng/ml) by developed nanosuspension. The formulation was safe as no animal loss or distinct change in cell morphology or intrinsic toxicity was observed in experimental animals. The formulation served as a novel approach for drug administration to combat symptomatic relief from AD (Bhavna *et al*., 2014).

Li *et al*. (2018) developed meloxicam nanosuspensions for reduction in brain that efficiently reduced inflammation in brain cells. Meloxicam embedded bovine serum albumin suspension was formulated through acid/base neutralization method. Uniformly dispersed biphasic suspension consisted fine particles of mean size 78.67 nm that were physically stable with 6 months shelf-life. Spherical, smooth, and regular surface coating of bovine-serum albumin over drug particles (mean particle size = 78.67 ± 0.22 nm) was revealed by transmission electron microscopy. The pharmacokinetic parameters, half-life, mean residence time, and AUC0-∞ got improved by 169.8%, 150.1%, and 148.8% after intravenous administration. Though the authors did not prove its utility in AD therapeutics, they claimed its usefulness for symptomatic relief in neurodegenerative disorders. The concentration of meloxicam was found to be higher in inflamed brain tissues after injecting a nanosuspension in Sprague Dawley rats left and right paws. The graph plotted between concentration of drug in endothelial cells and time exhibited higher meloxicam concentration (~450 ng/ml) from nanosuspension compared to meloxicam solution (225 ng/ml) after 2 hours. The results exhibited novel application of bovine-serum albumin coated meloxicam for alleviation of inflammation in brain neurons.

RECENT UPDATES ON PATENTS AND CLINICAL TRIALS ON ALZHEIMER'S TREATMENT

Nanotechnology based dosage forms are being the most explored area for efficient delivery of the drugs for AD. The USFDA has recently approved Tauvid (flortaucipir F18) for i.v. injection, the first drug used to help image a distinctive characteristic of AD in the brain called tau pathology. Tauvid is a radioactive diagnostic agent for adult patients with intellectual impairment and is being evaluated for AD. Tauvid is suggested for positron emission tomography imaging of the brain to determine the distribution and density of aggregated tau NFTs, a primary marker of AD (USFDA, 2020). Luthman *et al*. (2019) patented methods for bringing down clinical reduction in an individual having early AD, methods of converting an amyloid positive individual during initial stages to amyloid negative, methods for lowering brain amyloid level in an individual, and methods of preventing AD, the methods comprising administering a composition comprising a therapeutically effective amount of at least one anti-Aβ protofibril antibody. Gelmont *et al*. (2019) have been assigned a patent which provides, among other aspects, methods for the treating AD in individuals in need thereof, the method including administration of a therapeutically effective amount of a pooled human immunoglobulin G (IgG) and/or an anti-beta amyloid monoclonal antibody composition to an individual having moderately severe AD.

Various patents have been granted/published in this field depending on the nanocarrier systems, including multiple dosage forms, liposomes, nanoparticles, solid lipid nanoparticles, nano-emulsion, etc., (Patel *et al*., 2017) which are compiled in Table 6. Castor *et al*. (2019) got patented an AD drug candidate, APH-1104, a potent analog of Bryostatin-1, and is neuroprotective by α-secretase activation via novel protein kinase C (PKC) isoforms, down-regulation of pro-inflammatory and angiogenic processes, and the substitution of β-amyloid for its soluble and harmless relative, sAPP-α at concentrations which are orders of magnitude lower than conventional APP modulators. These nanoparticles protect Bryostatin-1 in its transit to the stomach, are resistant to stomach acids, and increase residence time and efficacy once transported to the circulation system in the duodenum. Castor (2020) has been assigned a patent for the combination therapeutic consisting of nanospheres co-encapsulating Bryostatin-1 and a Retinoid to improve synergistically α-secretase production and reduce β-amyloid plaque generation. Bryostatin-1 stimulates the production of some isoforms of PKC which enhances the production of α-secretase resulting in soluble amyloid precursor protein, and inhibits the formation of β amyloid plaques. Retinoids such as all-trans retinoic acid (ATRA, retinoic acid) enhance α-secretase activity via increased levels of expressed ADAM10 protein.

Improvement in therapeutic mediation for treating individuals with AD is of prime importance for both clinicians and pharmaceutical industries. Hence collection and investigation of clinical information is required for designing new protocols and/or the advancement of upgraded therapeutics for treating the disorder. Table 7 presents a compilation of the drugs that are in phase III clinical trials, while the drugs utilized in phase II clinical trials are summarized in Table 8 (Romano, 2018).

FUTURE PERSPECTIVE

Nanocarriers seem to offer a novel way of facilitating research attempts by explicitly regulating various pathways in focused areas. An interesting target for the development of better AD therapeutics can be mitochondrial dysfunction. Magnetic NPs are a productive area for research and have numerous existing as well as potential technological applications. Dendrimers and nanoemulsions are also two classifications of nanoparticulate systems which ought to be investigated additionally for transport of CNS drug. A few issues are required to be resolved before nanomedicines for AD comes to clinical setting. They are (i) the general and the biggest hurdle is low targeting efficiency, which may restrict the therapeutic effect and cause harm to other organs and (ii) another concern is the distribution of nanomaterials into the brain. To attain specific targeting in the brain, sequentially targeted nanomaterials require consideration. Objective should be to target not only BBB, but to also target the diseased site, to prevent distribution in whole brain.

Various in vitro investigations have reported the potential adequacy of nanocarriers; however, future in vivo

Table 6. Patents on drug delivery systems based on nanotechnology for treatment of AD.

Patent number	Country of filling	Active ingredient/ Composition		Center point/ Main out come	Publication year/granted	Ref.
CA 02203513	Canada	Selegilin	Selegilin liposome for improved targeting via parenteral route and enhanced permeation in case of Transdermal delivery for AD treatment	2001	Mezei *et al*., 2001	
US 2006 0018839A1	USA	Cholinesterase inhibitors	Delivery of ChEIs through various delivery systems, through nasal and ophthalmic route to enhance targeting in AD and ocular disorders	2006	Ieni and Pratt, 2006	
267/KOLNP/2007	India	Glatiramer acetate (GA)	Nano-emulsion and Proteosomes for GA via parenteral route and nasal route for improving neuroinflammation in AD	2007	Maron *et al*., 2007	
US 2009 0252796 A1	USA	Nutritional supplement	Nutritional mixtures and food supplements prepared using microfluidizers for enhancing the status of AD patient.	2009	Mazed and Mazed, 2009	
WO 2009 150686A1	WIPO	Model drug	Liposomes with specific lipid contents having high binding capacity to decrease Aβ plaques in AD	2009	Masserini *et al*., 2009	
EP 2332570 A1	Europe	Glatiramer acetate (GA)	Nano-emulsion and Proteosomes for GA via parenteral route and nasal route for improving neuroinflammation in AD	2011	Frenkel *et al*., 2011	
US 2011 0045050A1	USA	Multiple therapeutic agent	Bioavailability of various therapeutic agents can be improved by prepared nano-emulsion	2011	Elbayoumi *et al*., 2011	
US 2013 8349293B2	USA	Metallic ions	Metal-based nanoparticles for diagnosis of AD by magnetic resonance imaging (MRI).	2013	Corot, 2013	
WO 2014 076709A1	WIPO	Model drug	Peptide conjugated liposomes for targeting in AD	2014	Allon *et al*., 2014	
US 2014 8877207B2	USA	Cerium oxide	Cerium oxide loaded polymeric nanoparticles containing antibody specific for Aβ embedded to provide improved targeting in AD.	2014	Cimini *et al*., 2014	
EP 2550020 B1	Europe	Metal ions and lipids	Reverse micellar system for enhanced targeting utilizing metal ions and various lipids	2015	Maurel, 2015	
US 2015 9192644B2	USA	Curcuminoid	The formulation contains curcuminoid SLN which are stable at basic pH and enhances the concentration in AD patient brain	2015	Frautschy and Gregory, 2015	
US 2015 0017235A1	USA	Model drug	Liposomes with specific lipids that can decrease Aβ plaques in AD	2015	Masserini *et al*., 2015	
US 2015 0086616A1	USA	NSAIDS	Intranasal NSAIDS for enhanced neuroprotection in AD using various nano-dosage forms	2015	Lehrer, 2015	
US10662226B2	USA	Synthetic beta-amyloid peptides	The synthesized Aβ peptides can form stable, soluble oligomers that are useful for the advancement of knowledge, diagnosis, and management of AD. Related antibodies (specific to oligomeric Aβ) and their developmental techniques are discussed.	2016	Nowick *et al*., 2016	
WO 2018 081460A1	WIPO	An anti-abeta protofibril antibody and a beta-secretase bace1 inhibitor	The novel antibody composition (at a dose ranging from 2.5 mg/kg to 10 mg/kg) is used for treating, preventing, and/or delaying the onset and/or development of AD.	2018	Satlin and Fukushima, 2018	
WO 2018 197383A1	WIPO	Idalopirdine, Baclofen and Acamprosate	Novel combined therapeutic, their salts and prodrugs were invented for the management of AD.	2018	Cohen *et al*., 2018	
WO 2018 148821A1	WIPO	Ginseng and ginsenosides	Active combination of ginseng and ginsenosides for improved cognition behaviour and bioavailability in brain cells.	2018	Kay and Maclellan, 2018	
10485766	USA	Nanoparticles	In this invention, Bryostatin-1 oral nanoparticles were developed claiming rapid restoration of cognitive performance in Alzheimer's transgenic mice.	2019	Castor *et al*., 2019	
EP2994160 (B1)	Europe	IgG and/ or anti-beta amyloid monochlonal antibody	Present study claims treatment of AD (subject carrying ApEO4 allele) with therapeutically effective amount of pooled immunoglobulin G and/or anti-beta amyloid monochlonal antibody for the period of two weeks.	2019	Gelmont *et al*., 2019	
WO 2020 023530A3	WIPO	Anti-Aβ protofibril antibody	The invention claims effective administration of a composition comprising a therapeutically effective amount of anti-Aβ protofibril antibody for the treatment of AD. The focus of invention is to convert amyloid positive subjects to negative in early Alzheimer case.	2019	Luthman *et al*., 2019	
10,828,276	USA	Bryostatin-1 and Retinoic acid	Nanospheres co-encapsulating a Bryoid and a Retinoid to improve synergistically alpha-secretase production and reduce beta-amyloid plaque generation.	2020	Castor, 2020	

studies of these nanocarriers can possibly disclose a long-term systemic efficacy or potential toxicity in biological systems which can be correlated with *in vitro* systems. Despite the fact that the registration of patents related to nanotechnology-based systems is presently rising, clinical studies are required to assess their clinical efficacy and potential toxicological effects in humans. A detailed focus on the stability and safety in terms of biological retention, exposure time, nanocarrier size, dose, and metabolites of various polymers of the nanocarriers is also required. Subsequently, an assessment of the safety and adequacy of appropriate nanocarriers by conducting clinical studies in humans can result in encouraging cost-effective AD therapeutics.

Table 7. Drugs used in phase III clinical studies for the treatment of AD patients.

Title of the study and/or Name of the therapeutic agent	Identifier no. of ClinicalTrials.gov	Therapeutic agent's biological classification	Patient group enrolled in the clinical trial	Current status of the clinical trial and results of previous trials, if applicable.
BHV-4157	NCT03605667	Small molecule designed for neuroprotection	Patients with mild to moderate AD	Active and not recruiting
BIIB092	NCT03352557	It is an anti-tau monoclonal antibody	Patients with early AD	Active and not recruiting
Exercise combined with Losartan, Amlodipine and Atorvastatin	NCT02913664	Physical activity along with small drugs to control high B.P. and hyperlipidemia	Senior adults at high risk for vascular dementia and/or AD	Active and not recruiting
Methylphenidate	NCT02346201	Small molecule designed to reduce neuropsychiatric symptoms related to apathy	Patients with Alzheimer's disease	Active and not recruiting
ALZT-OP1a / ALZT-OP1b	NCT02547818	ALZT-OP1a is anti-inflammatory and anti-amyloid. ALZT-OP1b is anti-inflammatory. Both of these are small molecules.	Patients with early AD	Active and not recruiting
Nabilone	NCT02351882	This small molecule is a cannabinoid designed to control neuropsychiatric symptoms and calm agitation.	Patients with moderate to severe AD	Completed

Table 8. Drugs used in phase II clinical studies for the treatment of AD patients.

Title of the study and/or Name of the therapeutic agent	Identifier no. of ClinicalTrials.gov	Therapeutic agent's biological classification	Patient group enrolled in the clinical trial	Current status of the clinical trial and outcomes of previous trials, if applicable
COR388	NCT03823404	Anti-inflammatory	Patients with mild to moderate AD-related dementia	Recruiting
AMX0035	NCT03533257	Neuroprotective small molecule designed to inhibit mitochondrial and endoplasmic reticulum stress	Patients with AD-related early dementia, or late mild cognitive impairment	Active and not recruiting
AstroStem	NCT03117738	Mesenchymal stem cells derived from autologous adipose tissues	Patients having mild-to-moderate AD	Completed
Cilostazol	NCT02491268	Small molecule designed to act as an anti-platelet agent by inhibiting phosphodiesterase-3 (PDE-3). It is a neuroprotective factor that reduces the accumulation of amyloid deposits and the phosphorylation of tau protein	Patients with AD and with mild cognitive impairment	Active and not recruiting
S47445	NCT02626572	Neurotransmitter	Patients with AD, who are affected by mild to moderate depressive symptoms.	Completed.

CONCLUSION

Significant advancement has been achieved in AD therapeutics, but the entire currently available approaches target on mitigating symptoms instead of curing, implying that AD can still be considered as an unresolvable neurodegenerative disorder and needs interim advancement. Nanotechnological applications offer a lucrative efficient strategy for the AD treatment. A plethora of nanocarriers have been developed that have ability to cater to the limitations of conventional therapy, can assist in preliminary diagnosis, enhance therapeutic efficacy and bioavailability, offer negligible cytotoxicity in animal models, and present newer possibilities for development of superior formulations of potent drugs intended for AD therapeutics.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

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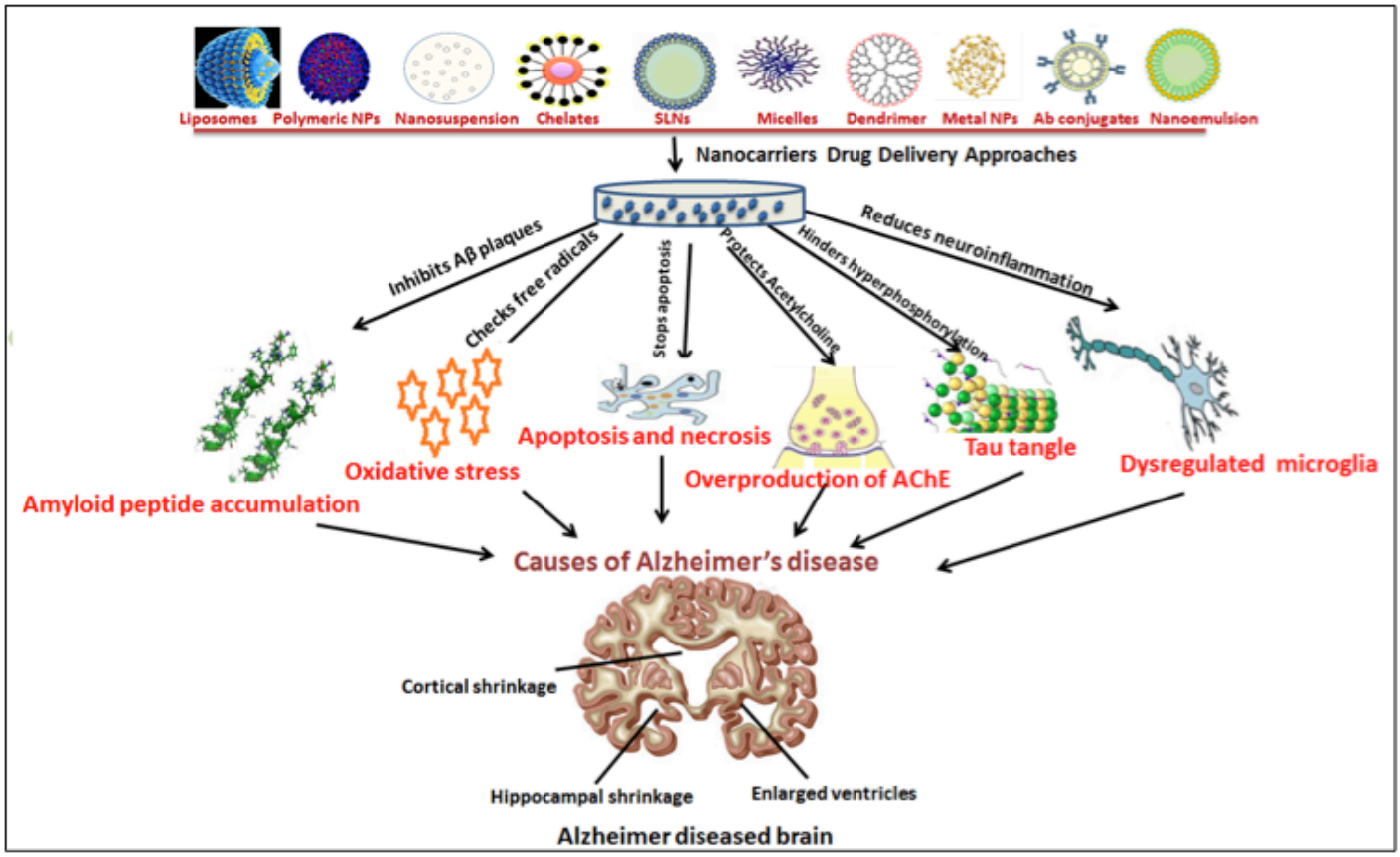
GRAPHICAL ABSTRACT



Clinical Management Updates for Novel Corona Virus (COVID-19)

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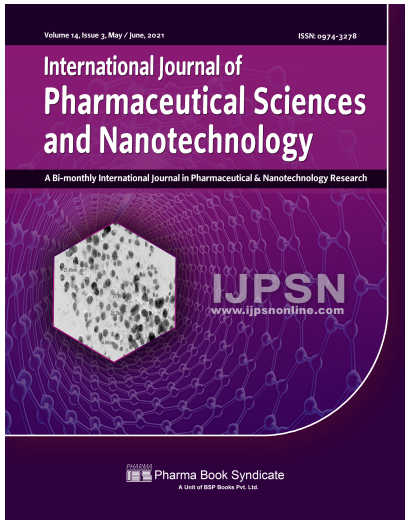

ABSTRACT

The SARS-CoV-2 virus was first detected in Wuhan, China in December 2019 and was known to produce acute severe respiratory illness in humans which rapidly spread almost throughout the world within a few months. This human coronavirus has seven strains and they commonly produce illness in the nervous system, respiratory system and hepato- intestinal systems. This present review is an attempt to illustrate recent reports

pertaining to the management of SARS-CoV-2. Further, it also highlights the diagnosis and clinical management of COVID-19. Various search engines like Scopus, Pubmed and WHO databases were accessed and literature on current advances about COVID-19 including structural features, replication, possible pathogenic, symptoms, diagnosis, prognosis, methods of prevention and possible therapeutic agents used for treatment of patients was reviewed. Current studies indicate that COVID-19 is very infectious with droplet transmission potential. The key modalities to prevent the infection is by keeping social distancing, respiratory/hand hygiene, detection of infection and subsequent quarantine of the infected persons. Presently, either no vaccine for prevention or specific treatments available, however, COVID-19 patients may be managed by using some repositioned drugs and symptomatic treatment.

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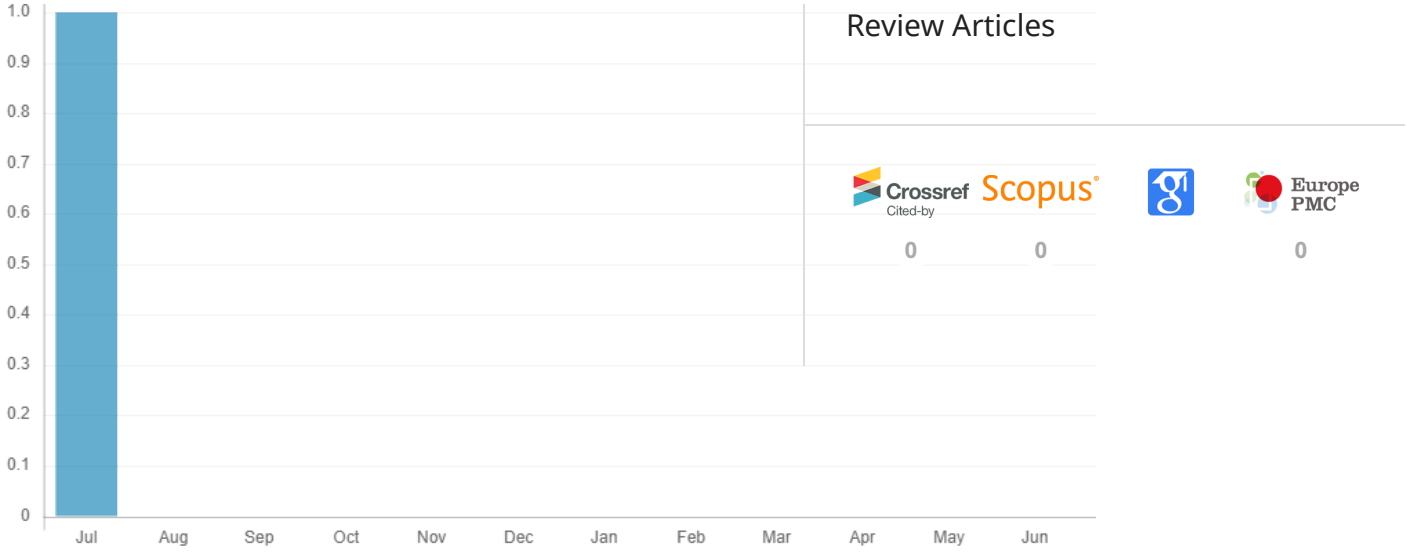

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KEYWORDS: COVID-19, Symptoms, Diagnosis, Prevention, Cure, Clinical Management

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An Update on Assessment, Therapeutic Management, and Patents on Insomnia

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Abstract

Insomnia is an ordinary situation related to noticeable disability in function and quality of life, mental and actual sickness, and mishappenings. It represents more than 5.5 million appointments to family doctors every year. Nonetheless, the ratio of insomniacs who are treated keeps on being low, demonstrating the requirement for proceeding with advancement and dispersal of effective treatments. Accordingly, it becomes significant to provide a compelling treatment for clinical practice. It indicates a need for the determination of various critical viewpoints for the evaluation of insomnia along with various accessible alternatives for treatment. These alternatives incorporate both nonpharmacological therapy, specifically cognitive behavioural therapy for insomnia, and a number of pharmacological treatments like orexin antagonists, “z-drugs,” benzodiazepines, selective histamine H1 antagonists, nonselective antihistamines, melatonin receptor agonists, antipsychotics, antidepressants, and anticonvulsants. Besides in individuals whose insomnia is due to restless leg syndrome, depression/mood disorder, or/and circadian disturbance, there is insignificant proof favouring the effectiveness of different prescriptions for the treatment of insomnia though they are widely used. Other pharmacological agents producing sedation should be prescribed with care for insomnia therapy because of greater risk of next-day sleepiness along with known adverse effects and toxicities. This review is also aimed at providing an update on various patents on dosage forms containing drugs for insomnia therapy.

1. Introduction

Insomnia is one of the most widely recognized issues experienced by the medical practitioners, accounting for more than 5.5 million prescriptions yearly [1]. Insomnia has been defined by the American Academy of Sleep Medicine to be the individual observation of trouble related to onset of sleep, time span, consolidation, or quality that come about regardless of sufficient time for sleep and that outcomes in some type of mental and physical unfitness during daytime [2–5]. Insomnia is a typical circumstance with prevalence point of approximately 10% in general population [6–9]. It is related to at least one of the following symptoms: trouble in sleep initiation (initial insomnia or sleep-onset insomnia), trouble in maintaining sleep (middle insomnia or sleep-maintenance insomnia), and early-morning arousing along with problem to get back to sleep (late insomnia) [4, 10].

There is a tremendous rise in the number of patients visiting physicians for insomnia from 5.3 million in 1999 to 208 million in 2010 [1]. The possibility of females experiencing insomnia is greater as compared to males, and they are two times as liable to be diagnosed with sleep disorders [8, 11]. In case of females, the hormonal changes, generally in the third trimester of pregnancy and postmenopausal changes, are also responsible for increasing the frequency of insomnia [8]. Though insomnia is especially common in elderly individuals, with indications found in almost 65% of people 65 years or older, it can occur at any age [12, 13]. Patients with concomitant diseases like respiratory problems, cardiovascular diseases, painful conditions, and neurological illness are at greater risk [14]. Population studies propose that it is highly predominant in individuals who are separated, unemployed, have encountered the demise of a family member, widowed, divorced, or of lower financial status [15–17]. It is also highly reported in individuals withdrawing from narcotics or alcohol.

In most of the instances, insomnia occurs concomitantly with physical or psychiatric problems. The relation between insomnia and the above conditions are complicated and at times bidirectional [18–21]. Indeed, insomnia can be a risk factor for nervousness, major depression, diabetes, hypertension, substance use disorders, and suicidal tendencies [22–28]. In addition to these factors along with the fact that insomnia results in decrement in life quality and a greater risk for falls and accidents, it is suggested the therapy should be specific for treating the insomnia once diagnosed, even if it occurs along with psychiatric or physical conditions [29, 30]. More than 80% of adults are affected every year by occurrence of short-term or acute insomnia. Chronic insomnia (more than 3 months of time span) is characterized by trouble in onset of sleep, inadequate sleep, or nonrestorative sleep resulting in complaints of daytime sleepiness, irritability, exhaustion, or problem in focusing and carrying out day-to-day work [31]. For individuals meeting the symptomatic basis for insomnia, various scientific therapies can be

approached including nonpharmacological as well as pharmacological therapies [32–34]. The suggested first-line treatment for insomnia is nonpharmacologic, like sleep restriction, relaxation training, and stimulus control. Drugs used for the treatment of insomnia are categorized as sedatives, hypnotics, drugs inducing sedation as a side effect, the drugs used in the treatment of insomnia-inducing sleep diagnoses like restless leg syndrome (RLS), and medicines regulating the sleep-associated circadian neuroendocrine system [35–37]. The impact of this disorder on public health with regard to frequency, morbidness, and effects on health and quality of life strictly requires its effective diagnosis and treatment in the clinical practice. This objective of this article is to review the diagnosis and treatment strategies for insomnia [34].

2. Pathophysiology of Insomnia

Various factors usually responsible for insomnia are psychological, physical, biological, environmental, and their interactions. Insomnia is frequently believed to be a disease related to hyperarousal [38], or enhanced cognitive, somatic, and cortical activation [39]. Patients with insomnia may encounter physiologic hyperarousal in both peripheral and central nervous systems. Hyperarousal can also be indicated as emotional and cognitive processes, with few theories recommending that affective and cognitive hyperarousal at sleep time may result in both acute and chronic insomnia [40]. Hyperarousal can be determined by measuring EEG, variability in heart rate, raised cortisol, or even self-report.

2.1. Genetics Involved in Sleep and Insomnia

Sleep and wake attributes, for example, sleeping time and duration, are hereditary [41] and controlled by various genes [42]. Involvement of genetic mechanisms in the etiology of insomnia is also implicated in animal and human investigations. Volunteer's gene assessment has recognized gene variants that might be engaged in the pathophysiology of insomnia, such as $PER3^{4/4}$ [43], homozygous Clock gene 3111C/C Clock [44], Apoε^4 [45], short (s-) allele of the 5-HTTLPR [46], and HLA DQB1∗0602 [47]. A study based on genomes revealed various single-nucleotide polymorphisms considerably related to insomnia symptoms [48]. The most considerable single-nucleotide polymorphisms found within genes are associated with stress reactivity (e.g., STK39, USP25, and MARP10), neuroplasticity (e.g., ROR1, PLCB1, EPHA4, and CACNA1A), mental health (e.g., NPAS3), and neuronal excitability (e.g., GABRB1 and DLG2) [48].

As a whole, the abovementioned evidences suggest considerable heritability and involvement of multiple gene in the pathophysiology of insomnia. Genes most consistently found to be related to insomnia are genes linked to sleep-wake

processes, arousal regulation, and brain functioning. The unpredictable interplay of these genes is responsible, at least to a limited extent, for the heterogeneity discovered in insomnia indications and outcomes. Future hereditary investigations with thorough evaluation of health and sleep history of individuals with chronic insomnia problem may additionally refine our comprehension of hereditary components associated in the characteristics and development of insomnia.

2.2. Molecular Mechanisms of Sleep and Insomnia

Various substances regulating sleep are connected to sleep regulation and circadian rhythmicity. In spite of perceiving the oversimplification [49], it is contended that endogenous substances are classified mainly as wake-suppressing/sleep-promoting (such as *γ*-aminobutyric acid [GABA], prostaglandin D2, serotonin, adenosine, and melatonin) and sleep-suppressing/wake-promoting substances (like orexin, catecholamines, and histamine). A smaller number of molecular investigations were performed on insomnia, and only a few molecules have been focused (e.g., cortisol and GABA) [50]. Results are mixed across investigations, without any steady pattern for a particular kind of molecule (wake versus sleep-inducing) has arisen. In spite of conflicting evidence, findings have mainly been deciphered with reference to hyperarousal model. For instance, raised [51] and decreased [52] levels of GABA in the occipital cortex of individuals with insomnia were found to be compatible with the hyperarousal hypothesis of insomnia. Nevertheless, sleep regulatory molecules link with one another unpredictably, and large number of their impacts are reliant upon the milieu of the brain state, i.e., they are state-dependent. The abovementioned parameters make it unpredictable that all instances of insomnia can be described by changes in any one kind of molecule (e.g., hyperarousal-related). Further refined conceptualization states that chronic insomnia develops from fragmentation of the alternating rhythms of sleep-regulatory and wake-promoting molecules in the brain [53].

Humans respond with different patterns in body temperature alterations, feeding, sleeping, and other biological functions to cycles of light and dark. The light signals received by the retina are translated by the pineal gland into a language understandable to the rest of the body, for example, via the synthesis of the hormone melatonin generally produced and released at night and thus regulating the metabolic activity of the body during sleep. The synthesis of melatonin and its release in the pineal gland are also regulated by another hormone norepinephrine. Norepinephrine functions by binding to its receptors in cell membranes. Earlier, it was thought that all these norepinephrine receptors acted independently of other proteins. However, in the recent investigations, it was found that this is not the case. Actually, these receptors collude with other dopamine receptors to form “heteromers.” Now, if dopamine binds with its receptors, it results in inhibition of norepinephrine effects, i.e., a reduction in the production of melatonin and its release. Incidentally, it was found that these

dopamine receptors become visible only in the pineal gland near to the end of the night, as the dark phase diminishes. Thus, it was concluded by the researchers that the heteromer formation is an effective mechanism to halt melatonin production as the day starts and to "wake up" the brain. "These findings are fascinating as they revealed a mechanism by which dopamine, generally raised at times of stimulation, can directly hinder production and release of a hormone, melatonin, responsible for inducing drowsiness and prepares the body for sleep" [54].

3. Classification of Sleep Disorders

The primary classification of sleep disorders, the Diagnostic Classification of Sleep and Arousal Disorders, published in 1979 [55], classified sleep disorders into symptomatic classes forming the ground for the current classification systems. The International Classification of Sleep Disorders (ICSD) was first published in 1990. The ICSD classification, prepared mainly for epidemiologic, diagnostic, and at the point, research intention, has been broadly utilized by researchers and has permitted greater international correspondence in research related to sleep disorders [56]. The ICSD underwent minor updates and alterations leading to version 2 (ICSD-2) in 2005. The ICSD-2 classified the 81 major sleep disorders in eight significant classes. On the same basic outline as the ICSD-2, ICSD-3 was prepared, identifying seven major categories as follows [57]:

(1) Insomnia

(2) Sleep-associated breathing disorders

(3) Central disorders of hypersomnolence

(4) Circadian rhythm sleep/wake disorders

(5) Parasomnia

(6) Sleep-associated movement disorders

(7) Other sleep disorders

The disease insomnia can be classified as primary and secondary insomnia. Though the etiology of primary insomnia includes both intrinsic and extrinsic factors associated, yet they are not viewed as being secondary to another problem. Secondary

insomnia mainly occurs due to manifestations of a psychiatric or medical disease, another sleep problem, or drug addiction [58]. Though primary insomnia can appear in any individual, chronic insomnia mainly develops in a subgroup of people having fundamental inclination to insomnia [59]. Chronic insomnia is distinguished by indications that appear at least 3 times in a week for at least 3 months. Insomnias that remain for less than 3 months are termed as short-term insomnia. In few instances, individuals may display insomnia indications not fulfilling the basis for short-term insomnia and so require different kinds of therapy and is termed as other insomnia [60].

Though insomnia can be distinguished by various methods, most diagnoses can be classified as one of two categories [61]:

(1) Sleep-onset insomnia is associated with problem in getting asleep. It mainly appears in individuals who have a hard time relaxing in bed, and also individuals whose circadian rhythm disturbs because of factors like jet lag or unpredictable work schedules

(2) Sleep maintenance insomnia is associated with problem in continuing asleep after initial sleep onset. It mainly occurs in elderly people, along with persons who intake caffeine, tobacco, or alcohol before bed. Some diseases like sleep apnoea and RLS can also result in sleep maintenance insomnia

Few patients may have blended insomnia including both sleep-onset and sleep maintenance problem, and persons with chronic insomnia may feel that these indications shift over time.

4. Diagnosis

Insomnia is a sleep disorder in which a person is not able to complete his sleep due to various reasons which differ from person to person [62, 63]. The most common symptom generally witnessed is lack of concentration, loss of memory, decreased occupational, and social performance, aggression, irritation nature, and fatigue, etc. [4, 5, 35]. It is diagnosed on the basis of the trouble in falling sleeping, disturbance in continuing sleep, or awakening in early morning [5].

4.1. Diagnostic Tests for Insomnia

4.1.1. Sleep Diary

A sleep diary is a patient's sleeping and awaking time record with concerned information, usually over a period of several weeks. It is made by person and physician to record the sleeping arising time [64, 65]. This is an important tool for diagnosis of insomnia by using sleep diary which helps in suitable treatment to the patients.

4.1.2. Epworth Sleepiness Scale

The daytime sleepiness is measured by using Epworth sleepiness scale (ESS) with the help of short questionnaires. The possibility of falling asleep from 0 to 3 for eight different conditions is estimated by help of ESS. The scores for all the eight questions are calculated to obtain a single value. A score which lies in the range of 0–9 range is considered to be normal; while a score lying between 10–24 indicates sleep disorders [66].

4.1.3. Actigraphy

It is used for recording human nonfunctional and functional activity cycles [67]. Actigraphy has a small altigraph part called a sensor of actimetry. It is used to measure gross motor action for a week or more. It is a wristwatch-like unit worn on the wrist [68].

4.1.4. Athens Insomnia Scale (ASI)

It is most commonly used for diagnosing insomnia. It has 8 parameters in which 1 to 5 are related to nocturnal sleep, and 6, 7, and 8 parameters are associated with daytime dysfunction. ASI parameters include sleep promotion, awakening during the night, final awakening, total sleep duration, sleep quality, wellbeing during the day, functioning capacity during the day, and sleepiness during the day [69, 70] (as shown in Table 1).

Table 1. Athens insomnia scale.

Assessment parameters	**Sleep difficulty experienced at least three times per week**			
	0	**1**	**2**	**3**
Sleep induction	No difficulty	Moderately delayed	Remarkably delayed	Extremely delayed or did not sleep at all

Assessment parameters	Sleep difficulty experienced at least three times per week			
	0	1	2	3
Arousals during night-time	No difficulty	Insignificant difficulty	Considerable difficulty	Serious difficulty or did not sleep at all
Final arousal before scheduled time	Not before	Little earlier	Remarkably earlier	Very insufficient
Overall quality of sleep	Satisfactory	Slightly satisfactory	Markedly satisfactory	Very unsatisfactory
Sense of well-being during daytime	Regular	Moderately declined	Remarkably declined	Extremely declined
Sleepiness during daytime	None	Moderate	Remarkable	Extreme

4.1.5. Laboratory-Based Polysomnography (PSG)

It is used for the diagnosis of obstructive sleep apnoea syndrome (OSAS). It can be used for diagnosing various sleep disorders like periodic limb movement disorder, chronic insomnia, narcolepsy, and REM sleep behaviour disorder [71].

4.1.6. ICSD-3 Technique

It is most commonly used classification system for sleep disorders, with diagnostic criteria for insomnia disorder summarised [61, 65, 66]. Individuals with chronic insomnia frequently suffer from concomitant mental disorders which do not get easily diagnosed [72].

4.1.7. Multiple Sleep Latency Test (MSLT)

It is an insomnia diagnostic tool which is determined as the time elapsed from the start of a daytime nap period to the first signs of sleep called sleep latency. It is used to discriminate between physical tiredness and really extreme daytime sleepiness.

Its focus is to find the mode of falling asleep in relation to REM sleep and other brain patterns. It is also used to recognize and distinguish among numerous sleep complications [73].

4.2. Clinical Assessment of Insomnia

4.2.1. Chief Complaint

Insomnia is caused by various variables factor. These complaints can be completely separated into nighttime and daytime. The chief complaint of patient should be assessed about initiation as well as maintaining sleep, early daytime arousal, or just unrefreshing sleep is the chief complaint associated with insomnia [74].

4.2.2. Examination of Medical Patient History

Patient medical history related to insomnia with short sleep period has been related to various diseases like type II diabetes, hypertension, and more terrible neurocognitive dysfunction. Consumption of alcohol is a usual maladaptive self-treatment approach by individuals having insomnia and can even contribute during sleep-maintenance problems. Therefore, alcohol consumption is being measured or evaluated and considered during treatment planning. Many times some drug interaction can also lead to insomnia so it must be evaluated in patient medical history in order to know whether the patient is suffering from any other disease (Table 2) [57].

Table 2. Diagnostic management of insomnia.

Medical history and examination	1. Whether patient suffered with any neurological disorder such as amnesia, dementia, and epilepsy 2. Previous and current somatic disorder 3. Medication, alcohol, and caffeine 4. Circadian makers
Psychiatric psychological history	1. Previous and current mental disorder 2. Current and previous work condition

	3.	Personality confliction
Sleep history	1.	Circadian clock
	2.	Sleep disorder history

4.2.3. Sleeping History

The sleeping history incorporates sleep and awakening schedule, bedtime schedule, night-time behaviour, and dysfunctioning during day. It is very important to determine the previous and current sleep history of patient. It is very useful for the treatment of insomnia patient. There are several questions which may help to determine sleeping history as follows [75].

(1) Sleep and Wake Schedule. It must be determined in work, school days, and weekends or vacations. A detailed note on schedule to bed, time to sleep, recurrence of night arousals, time to get back to sleep, time awakening in the morning, and time to get out of bed [76].

(2) Bedtime Routine. To confirm the clinical assessment of insomnia, it should be ensured that deficient sleep is not because of poor sleep environment. A detailed study on the bedtime routine is main part used during the treatment phase of insomnia [70].

(3) Nocturnal Behaviour. The many questions arise about nocturnal behaviour such as what the patient is doing while not sleeping at night? Are there other behaviours during night, like leg kicking or snoring which necessitates alternative or collateral diagnosis? Also, contribution from a bed partner can be useful. An individual who reported to be awakened the whole night, his bed partner will regularly notice longer duration of sleep, recommending there might be some sleep state misconception [77].

(4) Daytime Functioning. The daytime functioning can induce insomnia because person becomes tired, heaviness head, headache, and feel uncomfortable in daily routing. Hence, daytime function must be considered in clinical assessment of insomnia [78].

5. Management of Insomnia

Once a person is determined to be suffering from insomnia, and treatment might be started with one of various accessible mediations. They can be mainly classified into nonmedicated therapies and pharmacological treatment along with fewer herbal treatments [34].

5.1. Nonmedicated Therapies

Various nonmedication treatment regimens are available which have been tried and executed for the treatment of insomnia. In this section, the components assisting the nonpharmacological therapy having the greatest experiential background and most extensive use, i.e., cognitive behavioural therapy for insomnia (CBT-I) are reviewed [34].

5.1.1. Sleep Hygiene and Cognitive Behavioural Therapies

Any patient suffering from insomnia should be asked for his sleep behaviours because sleep hygiene along with CBT-I can be used to treat insomnia without medications. Utilized in a number of patterns, CBT-I has been discovered to be successful in bringing down insomnia and improvement in sleep in a broad range of clinical populations [79–85]. Thus, the American College of Physicians has suggested this therapy to be the primary treatment for patients with insomnia [83] as this can avoid probable side effects and toxicities due to medicines and found to have long-lasting resolution in treatment of chronic insomnia that might give superior results as acquired from drug therapies [86]. Sleep hygiene signifies absence of required sleep accelerating approaches, drugs, dietary components, and environmental factors that can cause insomnia. Various drugs inducing insomnia are activating agents of prescription and abuse, weight loss preparations, nicotine, and caffeine.

Sleep hygiene can improve sleep by affecting sleep latency and time awake after sleep onset, total sleep time, and slow wave sleep; and influencing REM sleep. Some of the sleep hygiene recommendations are exercise, limiting caffeine, avoiding alcohol, food and liquid intake, bedroom environment, etc. The various advantages of exercise can decrease in sleep latencies and time awake after sleep onset; increase in total sleep time and slow wave sleep; and a slight delay, and minimal reductions, in REM sleep [87].

Caffeine intake before bedtime results in prolonged sleep latency, reduced total sleep time, and decrease in slow wave sleep; usually in a dose–response manner [88]. Alcohol being a sedative can be an appealing hypnotic [89]. Ebrahim and colleagues

[90] reviewed that though alcohol intake can reduce sleep onset latency and a more consolidated first half sleep, it is also related to an increase in disturbed and fragmented sleep in the second half of sleep. Furthermore, though low and moderate doses show little effect on REM sleep, high doses can remarkably reduce REM, mainly in the first half of the night.

Sleeping hungry or eating a heavy meal before sleep is generally not recommended, and also, liquid intake should be minimized in the evening (2–3 h before bedtime). Obviously, it suggests that trying to sleep can become more challenging if a person is digesting a heavy meal, particularly if it contains high levels of fat or spice. Moreover, sleeping hungry may sometimes result in decrease in blood sugar in the night, keeping the individual awake. Excess amount of liquid during the evening may result in increased urination resulting in increased nocturnal awakenings [91].

The sleep environment should be quiet, dark, cool, and comfortable, and more recently, free from electronics. In a study on Europeans, it was recommended that a hot bedroom or an uncomfortable bed can result in nonrestorative sleep [92]. Environmental modifications such as eye masks, blackout blinds, earplugs, use of suitable sleepwear, and bedding and new mattresses are encouraged under this recommendation. Both excessively hot and colder environments in the bedroom can negatively influence sleep. An ideal sleep temperature between 60°F/15.6°C and 67°F/19.4°C is suggested by the National Sleep Foundation [93]. Lights in the bedroom may prevent a person from sleeping or make him awake earlier than desired because of its influence on the circadian system and the melatonin suppression. Bedroom noise has been the most studied bedroom environmental factors [94]. The findings are clear in that excessive noise disrupts sleep and subsequent daytime performance, even if the person does not recall awakening during the night [94]. The WHO suggests night-time noise should be below 40 dB [95, 96].

CBT incorporates sleep hygiene in the utilization of sleep facilitating cognitive and behavioural approaches for the treatment of insomnia [97]. When CBT is provided by trained personnel for several extended appointments, it proved its usefulness in the treatment of chronic insomnia [98]. Though insomnia therapy can be restricted to the use of CBT and hygiene, yet this approach has some clear constraints. But these behavioural approaches are not recommended for treatment of acute and short-term insomnia with restricted value in treatment of insomnia with comorbidities. CBT-I needs patient interest and their efforts, but as a clinical approach, it may not be available to all affected persons because of both expense and constraints in provider availability [99]. Even if judiciously used, it may not provide relief to every patient [100]. CBT is generally given for about 4-7 sessions. However, still it is not clear that how many sessions are required for optimal benefit, it was found that less than four sessions will not provide the desired response [80, 101].

(1) Educational Components of CBT-I. Though most of the patients of insomnia are well known regarding the various behaviours that are included under the category of sleep hygiene, it is still necessary to educate them regarding the suitable conditions. These are the significance of providing a favourable sleep environment by maintaining darkness, peace, and coolness in the bedroom. Patients need to remember to avoid consuming sleep-disturbing substances, like alcohol, nicotine, and caffeine, especially before bedtime. Similarly, strenuous exercise should not be done at least three to four hours before bedtime. In addition, a relaxing schedule can be useful in preparing an individual for sleep including preventing arousing activities like exposing to bright light (like laptop screen), which can have negative impact on someone's circadian rhythm [34].

(2) Behavioural Components of CBT-I.

Stimulus Control. Awakening due to some conditions is one of the major parameter involved in the pathogenesis of insomnia. Vicious circle of the bedroom/bed and episodes of physiologic awakening, fright, nervousness, and irritation prompts the bed serving as the known indication or conditioned stimulus for awakening, which is not compatible with sleep onset and maintenance. To get out of this conditioned stimulus, individuals are advised to keep themselves away from the bedroom and bed if not feeling sleepy and sit quietly somewhere until the sensation of sleepiness returns. Also, at sleep time, the patients are advised to avoid going to bed till they feel sleepy. The bedroom and bed should be strictly used for sleeping and sex, i.e., the patients should not do any other activities in bedroom, like reading or watching television. At last, patients are advised to get up at the same time every morning, seven days/week, and leave the bed within 10 to 15 min after arousing [34].

Sleep Restriction. Tendency of the patients to remain in bed for some more time duration is the other common reason responsible for the evolution and preservation of insomnia. In support of this, a reasonable answer has been given that the patients want to "get" sleep at whatever point they can. But again, this excess duration in bed brings about conditioned arousal and interrupted sleep. To adequately do this procedure, patients should be given sleep diaries for at least one week (however, 2 weeks are favoured), thereby reducing the patient's time in bed to the total sleep hours. For example, if a patient's diary reported six hours of average total sleep time however a period of nine hours in bed (bedtime 9 pm and awakening time 6 am), then a new sleep timetable should give a time of six hours in bed (bedtime 12 pm and awakening time 6 am) [102].

Particularly, patients are advised not to go for sleep until the newly recommended sleep time and only when sleepy. The patient's chronotype should be taken into account while finalising his sleep opportunity window. A minimum time of 5 hours in bed has been mentioned in the literature because of safety reasons related to sleep restriction (for example, somnolent driving

and cognitive deficits) [102]. Also, sleep restriction may intensify comorbidities. For example, sleep restriction has been found to precipitate mania in individuals with bipolar disorder, lower seizure thresholds, and increase pain sensitivity [100, 103, 104].

Sleep diaries should be filled by the patients throughout the therapy. Their schedules regarding timings in bed must be evaluated in all successive CBT sessions, and each session should be scheduled after every one to two weeks. The physicians can determine patients' average sleep efficiency from the sleep diaries, calculated as the percentage of time a patient is asleep given his/her time in bed. An average sleep efficiency of 85% or more is preferred as a measurement for "good" sleep quality and an edge to be reached before modifying the time in bed proposal. Whenever it is confirmed that the sleep efficiency of patient is acceptably significant, the physician can increase the time in bed, especially by modifying the recommended bedtime by 15 min after each session and following the patient's improvement in subjective sleep quality and daytime sleepiness.

Sleep restriction is the part of CBT-I that mainly suffers due to patient's refusal. If a patient is not willing or unable to complete the recommended time in bed, sleep compression may be utilized. This approach comprises of gradual decrease in time in bed over time so that the original recommended time in bed can be met and might be more compatible with patients, especially those with higher nervousness about losing further sleep opportunity.

Relaxation and Paradoxical Intention. These behavioural approaches supplement sleep restriction and stimulus control by furnishing the patient with techniques to decrease arousal before bedtime and in case of awakenings during nighttime. Relaxation techniques vary, however, it includes the tensing and relaxing of muscle groups, diaphragmatic breathing, and potentially visual symbolism. Paradoxical approach is based on the concept that sleep onset is suppressed due to nervousness about getting asleep. Utilizing this approach, patients are advised to remain awake as long as possible, resulting in faster onset of sleep due to reduced nervousness.

(3) Cognitive Components of CBT-I. Abnormal thoughts and assumptions regarding sleep are especially considered throughout the therapy. Sleep-related concerns should be significantly attended by the clinician, as they will induce unsuitable behaviours that extend insomnia. These sleep-related worries include unrealistic assumptions regarding sleep and cataclysmic thoughts about the effects of sleep loss. One way for combating cataclysmic thinking is by assessing evidences from the experiences of patient. For example, if a patient thinks that a low sleep time during night will make him/her incapable to perform effectively in his/her work, then, a physician should ask the patient recognizing cases when he/she was able to perform adequately in spite of a poor sleep during the night. Moreover, equipping patients with techniques to decrease stress at bedtime can be useful.

Second approach, known as a constructive worry exercise, in which patients are required to make a list of at least three problems in the early evening which they think will make them awakened at night. The patients should mention a solution for every problem. The diary should be closed and kept away, and, now if patients wake up at night, they are advised to remind themselves that they have already resolved that issue at their "problem-solving best" (i.e., not in the midnight) [34].

5.2. Pharmacological Therapies

Irrespective of the kind of treatment given, the therapy of chronic insomnia has two key goals: improving quantity and quality of sleep and decreasing daytime impairments. Initial treatment strategies generally involve at least one behavioural mediation, like relaxation therapy or stimulus control therapy. In case pharmacotherapy becomes necessary, a particular medication within a class should be chosen as per the following directions: (1) pattern of symptoms, (2) objectives of therapy, (3) previous therapy responses, (4) cost, (5) patient compliance, (6) contraindications, (7) the accessibility of other medicines, (8) comorbidities, (9) possible adverse effects, and (10) simultaneous medication interactions [10].

This section reviewed the characteristics of all of these pharmacological agents (orexin antagonists, "z-drugs," benzodiazepines, selective histamine H1 antagonists, nonselective antihistamines, melatonin receptor agonists, antipsychotics, antidepressants, and anticonvulsants) (Table 3) and compiled the available evidences related to their efficiency and safety on the basis of which clinical decision can be made.

Table 3. Comparison of commonly prescribed medications for the treatment of Insomnia.

Class of drugs	Dosage (mg)	Approximate $t_{1/2}$ (h)	Approximate T_{max} (h)	Primary indication
Z-drugs				
Zolpidem, sublingual (Intermezzo)	1.75 or 3.5	2.5	1	Awakening in night
Zolpidem (Ambien)	5 to 10	2.6	1.6	Onset and maintenance of sleep

Class of drugs	Dosage (mg)	Approximate $t_{1/2}$ (h)	Approximate T_{max} (h)	Primary indication
Zolpidem, extended release (Ambien CR)	6.25 to 12.5	2.8	1.5	Onset and maintenance of sleep
Eszopiclone (Lunesta)	1 to 3	6	1	Onset and maintenance of sleep
Zaleplon (Sonata)	5 to 10	1	1	Onset of sleep
Benzodiazepines				
Triazolam	0.125 to 0.25	1.5 to 5.5	2	Onset of sleep
Estazolam	0.5 to 2	10 to 24	2	Maintenance of sleep
Quazepam (Doral)	7.5 to 15	25 to 84	2	Maintenance of sleep

5.2.1. Benzodiazepines

These drugs act by modulating the *γ*-aminobutyric acid (GABA) type A receptors in neurons causing activation of chloride channels that produces Cl^- ion influx and cell hyperpolarization [105]. GABA works as an inhibitory neurotransmitter in the CNS, diminishing neuronal excitability. By stimulating the GABA receptors, benzodiazepines cause sedation, diminished nervousness, retrograde amnesia, and muscle relaxation [18, 106]. Though various benzodiazepines are utilized in insomnia treatment, only five (triazolam, flurazepam, temazepam, quazepam, and estazolam) are authorized by the U.S. FDA for insomnia. A few significant differences should be considered while a benzodiazepine is being prescribed for insomnia, like onset, duration of action, and metabolism. Rate of metabolism is especially significant in individuals with compromised kidney and/or liver function or elderly patients as these drugs may cause bioaccumulation, leading to adverse effects like daytime sleepiness, loss of coordination, and memory impairment. In addition to these effects, long-term use of benzodiazepine will disrupt the sleep quality by deforming the sleep architecture and declining deep sleep duration, thereby justifying the point that patients taking benzodiazepines for long term reported much more tiredness than self-reported good sleepers [2].

There is a high risk of emerging physical dependence to benzodiazepines [107]; extreme withdrawal indications after cessation has been reported by 15% to 40% of chronic users [108]. Even there are cases, when patients often reported increased nervousness and rebound insomnia after only a few weeks of benzodiazepine treatment [109]. These drugs have shown contraindications during breastfeeding and pregnancy. Benzodiazepines should be avoided in persons having chronic pulmonary disease and/or sleep apnoea as they may cause suppression of respiratory drive. Benzodiazepines are categorized as schedule IV drugs, due to their abuse potential.

5.2.2. "Z-Drugs"

Zolpidem (Ambien), zaleplon (Sonata), and eszopiclone (Lunesta) are the most generally recommended category of medicines for insomnia, known as the z-drugs [110]. The efficacy of these drugs has been demonstrated in various trials including meta-analysis revealing that the sleep latency has been decreased by a mean value of 42 min versus 20 min for placebo [111]. The z-drugs bind in a similar manner as of benzodiazepines to the GABA-A receptor, resulting in cell hyperpolarization. But, the z-drugs as opposed to benzodiazepines bind with more specificity to particular subunits of the GABA-A receptor, basically focusing on the sedative effect of the receptor rather than the anxiolytic effect [112]. Various adverse effects of z-drugs especially in higher doses include gastrointestinal upset, dizziness, hallucinations, memory loss, and noninhibition. Sometimes, complex sleep-associated behaviours (for example, sleep eating, sleep driving) were found in persons using z-drugs in high doses; the patients should be informed regarding this risk initially while prescribing z-drugs [113–115]. The physician should also be known to the addictive potentials of these drugs as they may result in euphoria, anxiolysis, and stimulation in certain individuals, especially at higher doses [116]. These drugs have been utilized in the treatment of a wide range of sleep disorders without affecting sleep efficiency [107].

Zolpidem, an imidazopyridine used in the treatment of insomnia associated with problem of sleep latency and sleep maintenance, has also been used in the treatment of high-altitude insomnia and misalignment of circadian rhythm [117, 118]. Eszopiclone, a cyclopyrrolone drug due to its long half-life, has been utilized for the improvement of sleep latency, and it especially suits well for sleep maintenance [119]. But the only unfavourable aspect of eszopiclone is its unpleasant taste that influences almost 33% of patients at the maximum advised dose. A pyrazolopyrimidine drug, zaleplon, having very short half-life is recommended for the improvement of sleep latency but not sleep maintenance. All these drugs show a moderately distinct pharmacological profile, symptoms, efficacy, and adverse effects. These drugs can be prescribed during pregnancy just

if the advantages are more than the risks associated. Zolpidem, eszopiclone, and zaleplon are categorized as schedule IV drugs due to their abuse potential.

5.2.3. Melatonin Receptor Agonists

Melatonin is a hormone and is generally, secreted during the dark period of the day by the pineal gland. It plays a major role in maintaining the sleep-wake cycle, and disturbance in the melatonin release timings or diminished melatonin formation may result in insomnia and thus it is prescribed to many patients having insomnia. The issue becomes especially noticeable during shift work or when changing time zones. Production of melatonin also dwindles with age and might be partly accountable for the sleep problems encountered by elderly people [120]. Ramelteon (Rozerem) is a melatonin agonist authorized by the FDA for the treatment of sleep latency. Its efficacy is satisfactory with little adverse effects and the advantage of not habit forming [107]. A small investigation revealed that the drug has diminished the risk of hospital-related hysteria in elderly patients, bringing the rate from 32% to 3% in comparison to placebo [121]. This drug can be prescribed during pregnancy only if the advantages are more than the risks associated. For insomnia therapy, a sustained-release melatonin is considerably less costly and may be more efficacious as compared to ramelteon. A meta-analysis in 2013 revealed that melatonin in the dose range of 0.1 mg to 5 mg declined sleep latency by 7.1 min, enhanced total sleep duration by 8.3 min, enhanced overall sleep quality, and had a favourable adverse effect profile [122]. Since it is not governed by the FDA and purity fluctuates broadly among products, it is necessary to review product evaluations by third-party to assess the quality of the product.

The most widely recognized unfavourable effects of melatonin are headache, increase in reaction time, and may cause sedation during the day. It can be given to abuse-prone individuals with insomnia due to their nonabuse potential. Moreover, when given in high doses, it cans theoretical affect fertility as it is a hormone that controls reproductive function. Thus, ramelteon is not advised to those who are trying to conceive [123, 124]. It has a moderately benign adverse effect profile, among which the most generally revealed are nausea, fatigue, headache, and sedation. Because of its greater safety profile, it can be recommended for patients having problem in sleep onset only.

5.2.4. Selective H1 Antagonists

Doxepin in the dose range of 3-6 mg is the exclusively very selective histamine H1 receptor antagonist that has been consistently investigated [30]. Though the major potent pharmacological effect of doxepin is H1 antagonism, it originally

emerged as an antidepressant in the dose range of 75-150 mg/day [125]. Thus, with a decrease in the dosage, doxepin becomes a highly selective H1 antagonist [125]. Sedation during daytime is the most usual adverse effect disclosed in younger adults. On the other hand, elderly patients did not report any adverse effects with 3 mg of doxepin. And so, elderly patients with early morning arousal can be an especially appropriate group for treating with this drug. Due to its potent H1 antagonism, it can be recommended for patients having insomnia with allergy indications. Due to its nonabuse potential, doxepin can be given to individuals having difficulty in sleep maintenance and who are prone to addiction.

5.2.5. Orexin Receptor Antagonists

"Orexins" was the title given to two peptides that were comparatively recently found to emerge from the neurons of the lateral hypothalamus and to provoke arousal/wakefulness [126–128]. Orexin receptor antagonists are the agents that promote sleep because of its potential to obstruct the wakefulness provoked by the orexins. The first orexin receptor antagonist that got the approval for insomnia treatment is suvorexant (Belsomra). It causes blockages of both kinds of orexin receptors (orexin A and B). Sedation during daytime is the most usual adverse effect of suvorexant. Prior investigations revealed that some abuse potential is associated with this drug that is somewhat comparable to that of zolpidem. So, in patients predisposed to abuse, it is better to be avoided. It is an exclusive drug with therapeutic effects in the last third of the night without considerably enhancing morning sedation leading to strong therapeutic effect on sleep onset. Thus, suvorexant can be prescribed to those individuals having both difficulty in onset of sleep and arousal in early morning. However, it is not advised as a first-line therapy for insomnia due to its higher cost and abuse potential. Table 4 compiles significant orexin receptor antagonists that were developed/abandoned or are in developmental pipeline.

Table 4. Orexin receptor antagonists that were developed/abandoned/are in developmental pipeline.

Drug	Mechanism of action	Remark	Ref
Almorexant	An orexin antagonist that functions as a competitive receptor antagonist of the OX_1 and OX_2 orexin receptors	Development of the drug was abandoned in January 2011	[129

Drug	Mechanism of action	Remark	Ref
Lemborexant	Dual orexin receptor antagonist (DORA) of the orexin OX_1 and OX_2 receptors	Approved by the FDA in December 2019 and released on June 1, 2020, by Merck.	[130
Filorexant	DORA	Was under development by Merck for the insomnia treatment. As of May 2015, filorexant is no longer listed on Merck's online development pipeline.	[131
Nemorexant	DORA	In April 2020, first phase III clinical trial for daridorexant has been approved for insomnia treatment.	[132
SB-334,867	First nonpeptide antagonist emerged and is selective for the orexin receptor OX_1, having about 50 times more selectivity over OX_2 receptors	Studies in animals have shown sedative and anorectic effects.	[133
SB-408,124	Is a nonpeptide antagonist selective for the orexin receptor OX_1, having about 70 times more selectivity over OX_2 receptors.	Enhanced oral bioavailability in comparison to the older OX_1 antagonist SB-334,867.	[134

5.2.6. Antidepressants

There are some drugs initially used for the major depression therapy are now also utilized for the insomnia treatment. This category of drugs also produces improvement in sleep by obstructing the receptors for neurotransmitters that cause arousal, e.g., acetylcholine, serotonin, histamine, and norepinephrine [30]. The most commonly recommended antidepressants for treatment of insomnia are 15 mg of mirtazapine, 10-75 mg of doxepin, 50-150 mg of trazodone, and 10-100 mg of amitriptyline [30]. The adverse effects caused by antidepressants for treating insomnia may vary. Daytime sedation is commonly caused by all, while some may cause orthostatic hypotension. The major adverse effects of mirtazapine are enhanced appetite/weight gain and sedation. The amitriptyline and doxepin (25-50 mg) may cause cognitive impairment, blurred vision, dry mouth, arrhythmias, constipation, increased appetite/weight gain, and urinary retention [30]. Trazodone is responsible for causing adverse effects such as sedation and orthostatic hypotension and may induce priapism [30].

Due to their nonaddictive potential, all these drugs can be given to patients with an inclination to drug abuse. These drugs can also be prescribed to patients in whom the commonly used therapy failed or have associated conditions like nervousness, mood, and pain difficulties, due to their wide pharmacological outcomes [30]. Patients suffering from glaucoma, urinary obstruction, and cognitive impairment should be given doxepin and amitriptyline cautiously. All these drugs are troublesome in individuals with bipolar depression, due to the fear of accelerating mania [138].

5.2.7. Nonselective Antihistamines

Doxylamine and diphenhydramine are the two major nonselective antihistamines that are usually recommended for insomnia therapy. However, these are prescribed only for the therapy of pregnancy-related sleeplessness. Both of these drugs show clinically relevant M1 muscarinic cholinergic antagonism in addition to H1 antagonism. The major adverse effects of these drugs are dizziness, sedation, blurred vision, cognitive impairment, psychomotor impairment, dry mouth, weight gain, urinary retention, and constipation. More uncommon side effects of doxylamine reported are coma and rhabdomyolysis, whereas that of diphenhydramine is agitation and insomnia [139].

Due to their insignificant addictive potential, these drugs can be recommended for using in drug abuse-prone insomnia patients. These are also suitable for insomnia patients having upper respiratory infections or allergic symptoms. These medications should not be given to patients with urinary retention, chronic obstructive pulmonary disease, asthma, reduced gastrointestinal motility, and closed-angle glaucoma.

5.2.8. Antipsychotics

These are the category of drugs mainly used for treating the psychotic states that are occasionally also utilized for the treatment of insomnia, but at a dose lower than that usually used in the treatment of psychotic patients [30]. These drugs produce sleep-improving effects owing to their broad antagonistic effect on arousal-provoking neurotransmitter receptors, like serotonin, histamine, dopamine, adrenergic, and cholinergic receptors. The antipsychotic drugs that are recommended in the treatment of insomnia in clinical practice are risperidone 0.25-6 mg, olanzapine 2.5-20 mg, and quetiapine 25-250 mg. The major adverse effects of these drugs include agitation, sedation, tachycardia, orthostatic hypotension, dizziness, increased appetite/weight gain, dry mouth, akathisia, and constipation. Really concerning, however, undeniably more uncommon, is the

fear of tardive dyskinesia. In patients suffering from dementia, the high possibility of cerebrovascular episodes must also be considered.

Because of their nonaddictive potential, these drugs can be recommended to patients with an inclination to drug abuse. However, these drugs are most appropriate for insomnia arising in persons suffering from bipolar or psychosis diseases. Precautions must be taken, while using these medications in patients with closed-angle glaucoma, urinary retention, dementia, constipation, and hypotension or at risk for myocardial infarction.

5.2.9. Anticonvulsants

There are some drugs initially developed for the seizure therapy that are now also used for the insomnia management. Examples are pregabalin and gabapentin, and they produce therapeutic effects in insomnia by decreasing the discharge of norepinephrine and glutamate by acting on the alpha-2-delta subunit of N-type voltage-gated calcium channels [140, 141]. A clinical trial study in patients suffering from occasional sleep disturbance revealed that gabapentin in a dose of 250 mg at bedtime enhanced total sleep duration by 64 min on 1st day and 46 min on 28th day of the trial [142]. Pregabalin and gabapentin also showed therapeutic effects on sleep disturbance in patients suffering from generalized anxiety disorder, pain, epilepsy, and restless legs syndrome [143–145].

The major adverse effects of pregabalin are dry mouth, dizziness, sedation, appetite increase, and cognitive impairment whereas for gabapentin includes ataxia, dizziness, sedation, and diplopia. Gabapentin does not have any abuse potential, whereas pregabalin showed some significant addictive potential [146]. These drugs can be recommended to insomnia patients also suffering from pain, RLS, or partial seizures. Pregabalin can also be used in patients with alcohol use disorder for the treatment of insomnia [147, 148]. In case of patients with impaired renal function, both these drugs should be avoided.

6. Treatment Considerations for Specific Populations

6.1. Circadian System Disturbances

Sleep disorders associated with circadian rhythm are due to an imbalance between about 24 h endogenous circadian rhythm and the “normal” 24 h day/night cycle. In patients with circadian disturbance, melatonin may work as a hypnotic and can be a beneficial supplement in the therapy [149]. Ramelteon, a synthetic analog of melatonin, is available for prescription. Light

exposure and melatonin have been proved to be particularly effective for the treatment of Delayed Sleep Phase Syndrome (DSPS) mostly occurring in young adults and adolescents [149]. Patients with this condition have problem getting sleep at the desired bedtime and have delayed sleep between 2 am and 6 am and afterwards if their way of living allows, sleeping roughly for about 8 h, waking up in between 10 am and 2 pm. Patients suffering from DSPS frequently experiences long-term deficient sleep duration with all its daytime effects. Therapy includes bright light exposure at the right time in the circadian phase response graph.

Therapy includes providing 10,000 lx of light for half an hour on arousal and timely administration of melatonin in the early evening 3–6 h before sleep time (prior to dim light melatonin onset (DLMO)). Advanced sleep phase syndrome (ASPS) is the mirror image of DSPS in individuals having onset of sleep and arousal both few hours before time than required with the total sleep duration remaining almost usual. ASPS is more uncommon as compared to DSPS and mostly occurring in middle-aged to elderly patients. Similar therapy as that for DSPS has been applied with the timing of therapy intended to retard rather than forward the circadian rhythm. Persons working in shift are recommended melatonin for shifting the circadian rhythm of the workers as desired. If given prior to bedtime, it can improve the sleep quality in the early morning [150, 151].

6.2. Restless Legs Syndrome (RLS) and Periodic Leg Movement Disorder

RLS is a typical neurological condition distinguished by the desire to move, especially the legs, occurring mainly at rest in the evening or bedtime. The fundamental characteristics for diagnosing RLS are as follows:

(1) Desire to move the legs, generally followed by awkward and uncomfortable sensations in the legs

(2) Desire to move or uncomfortable sensations start or deteriorate with rest or inactiveness

(3) The desire to move or uncomfortable sensations are somewhat or completely relieved by movement

(4) The desire to move or uncomfortable sensations are unacceptable in the evening [152]

About 3/4 of the patients with RLS suffer from sleep disturbance and grievances of diminished life quality [153]. Most of the RLS patients suffer from recurrent periodic limb movements (PLMD) on polysomnogram. The PLMD/RLS has a hereditary basis and rises with age so that over 30% of individuals having age more than 80 years may fulfil the diagnosis criteria. PLMD/RLS is also

commonly found in patients with low serum ferritin levels (<50), children with AD/HD, in patients on medications like antihistamines, antiemetics and antidepressants, and in patients having renal failure [154]. The therapy of the sleep disturbance, basically onset of sleep, depends primarily on therapy of RLS instead of treatment of resultant insomnia. The primary initial medications for RLS treatment belong to dopaminergic agonists. Both ropinirole and pramipexole have been approved by FDA for RLS but in low doses as compared to that required in Parkinson's disease. Ropinirole is given in the range of 0.25 to 4 mg and pramipexole at 0.125 to 2 mg. Pramipexole may initiate remarkable drowsiness along with sleep attacks in certain patients [155]. Earlier, benzodiazepines like clonazepam have been used, but also temazepam.

6.3. Insomnia Associated with Sleep Apnoea and Its Therapy

A significant percentage of population has been affected with obstructive sleep apnoea (OSA) that causes daytime sleepiness. Both the severity of apnoea and the degree of daytime sleepiness influencing waking capacity can be adversely influenced by using sedatives concomitantly—especially ethanol and opiates [156]. In a subgroup of OSA patients, breathing disturbance results in intermittent sleep and insomnia. The therapy of OSA with positive airway pressure (PAP) can enhance quality of sleep for these patients [157]. But, for some other individuals, PAP therapy may intensify sleeplessness (especially in patients with co-morbid PTSD) [158].

6.4. Comorbid Psychiatric Disorders

Major depression, psychotic disorders, anxiety disorders, bipolar mood disorder, and Alzheimer's disease are the various psychiatric disorders generally comorbid with insomnia. A range of 50–75% of incidences of insomnia with these diagnoses was estimated [159]. The diagnosis of depression in which depression and insomnia have a bidirectional or circular correlation is the most well-known psychiatric association [160]. Several investigations revealed the risk of developing depression in insomnia patients. A wide investigation on young volunteers for a time span of 20 years predicted that 14 days of insomnia or prolonged further will cause major depressive episodes and disorders [109]. Reoccurring insomnia are the indications that an individual in remission from his depression can be at risk of a relapse [161]. Long-term insomnia issues can result in the continuance of depression. The problem is of specific significance in light of the considerable rate of residual sleep disruption in patients who were otherwise effectively treated for depression [111]. The relation between depression and insomnia will get complicated by the certainty that most of the commonly used antidepressants, particularly the selective serotonin reuptake inhibitors (SSRI's), can result in sleep disruption [162]. Individuals diagnosed with a psychiatric disorder and insomnia, therapy includes those also

prescribed for primary insomnia, either cognitive behaviour treatment (behavioural and psychological), pharmacologic treatment, or a blend of both.

Eszopiclone along with fluoxetine has been investigated in persons with major depression [163]. The combination was well tolerated and showed quick improvement in sleep along with a faster and greater antidepressant response. This does not propose an antidepressant effect of eszopiclone yet rather recommends that improvement in sleep has a favourable effect on depression. These findings provide support for the comorbid strategy for the therapy with two drug moieties as opposed to the conventional strategy of waiting for insomnia to recover because of treatment of depression. Combined therapy involving antidepressants and CBT for insomnia also suggested that the combined therapy is better than the antidepressants alone both in regards of depression outcome and insomnia outcome [164].

6.5. Comorbid Pain

Most of the patients have poor sleep due to chronic pain [165]. Pain can be a major symptom of most of clinical diseases however most frequently rheumatologic disorders, headache, and cancer. Chronic pain and sleep disturbance develop a cycle of pain resulting in inadequate sleep which further resulted in greater pain [166]. Comorbid pain can be managed by diagnosing the sleep problem, maintaining the sleep hygiene, and applying CBT approach followed by use of pharmacological agents for both insomnia and pain [98]. In case of rheumatologic diseases, treating sleeplessness with hypnotics or sedative antidepressants not only enhances sleep but also improves pain tolerance.

6.6. Other Comorbid Medical Conditions

Patients having respiratory disorders frequently have disturbed sleep. COPD patients often have interrupted sleep [167]. This can be improved by providing oxygen if hypoxia is the reason for the issue. Though OSA generally causes daytime sleepiness, it can also cause disturbance in sleep too [168]. Approximately one-third of asthma patients who are ineffectively treated have asthma attacks during night that may interrupt their sleep resulting in daytime sleepiness. Individuals with gastroesophageal reflux frequently get their sleep disturbed due to the reflux. Also, reflux can precipitate asthma attacks in weak patients. Individuals having last-stage renal disorders experience a number of sleep problems like sleep apnea, insomnia, and a high occurrence of secondary RLS with a high predominance [169]. Menopause can be related with sleeplessness which can be treated with hormones but also requires a hypnotic [170]. Parkinson's disease is related with crucial insomnia, as in case of

gastrointestinal disorders causing reflux and/or pain, enuresis and nocturia, and various sleep-related issues such as narcolepsy [3].

7. Herbal Treatments

7.1. Valerian

Since ancient Greek and Roman times, Valerian, a herbal product comprised of the roots of *Valeriana officinalis*, has been utilized for the insomnia therapy [171]. It works by interacting with GABA-ergic neurotransmission, resulting in sedation [172]. Though few investigations have reported that valerian is valuable for the insomnia therapy, others have not [173–175]. Evaluation of the accessible clinical results are complicated by utilization of variable amounts and different sources of valerian, small sample sizes, different results obtained, and due to high rate of withdrawal [171]. As a whole, the evidences for valerian as an alternative for insomnia therapy remains uncertain, and it is not advised to use in insomnia patients [114].

7.2. Kava

Kava, a herbal product obtained from a shrub (*Piper methysticum*) and cultivated in the Pacific islands, works by acting on both BZD and GABA binding sites, producing antispasmodic, anticonvulsive, central muscular-relaxant, and sedative impacts [176]. Kava-containing medications are utilized as alternative treatment for restlessness, stress, and nervousness—significant reasons for long-term insomnia [176]. Notwithstanding, like various herbal products, kava is not suggested for the chronic insomnia therapy due to absence of clinical efficacy and safety data [114]. Kava-containing products were found to cause severe liver injury as warned by the FDA in 2002 [177].

8. Approaches to the Patient

For the insomnia treatment, behavioural interventions can be the best approach. In case, pharmacological mediation becomes essential, a customized approach depending on the insomnia type is recommended. In case, the first approach is not effective, an alternate drug from a similar category or a different category can be used. However, few patients can tolerate various sedative drugs, including a z-drug and sedating tricyclic antidepressant, utmost care must be taken while recommending such combinations. Due to the fear of respiratory depression, individuals having possibility of nocturnal hypoxia or sleep apnoea

because of lung disorders must be examined by a sleep expert prior to prescribing sedatives. Benzodiazepines due to greater potential for abuse are usually not suggested. Even though benzodiazepines are to be used, they should be prescribed at the lowest possible dose for the shortest possible duration. Benzodiazepines, tricyclic antidepressants (except nortriptyline and low-dose doxepin), atypical antipsychotics, and z-drugs should not be given to patients with long-term nocturnal hypoxia, individuals with untreated sleep apnoea, and in older adults. Herbal drugs were also not proved to be very efficacious for the insomnia treatment [114].

9. Recent Updates and Patents on Insomnia Therapeutics

Lemborexant, a DORA that got approval in December 2019 for treating insomnia, was distinguished by trouble with onset of sleep and/or maintenance of sleep in insomniacs [178, 179]. The drug with a half-life of about 17-19 h diminishes sleeplessness and advances non-REM sleep without affecting REM sleep [180]. The drug was investigated in the SUNRISE trials [181] and reported a significant improvement in sleep onset and sleep maintenance in comparison to placebo. The commonly reported adverse effect in the SUNRISE trials was sleepiness [182, 183] without any respiratory issues. Volunteers with minor OSA did not encounter aggravating sleep apnoea, as determined by variations in peripheral oxygen saturation or apnea-hypopnea index [184]. Other orexin inhibitors in phase III clinical trials are seltorexant and nemorexant (daridorexant). Nemorexant is a DORA having 6 h of half-life. The commonly reported adverse effects were somnolence, diarrhoea, fatigue, and headache [185, 186].

Seltorexant is a selective orexin-2 receptor antagonist with 2-3 h of half-life. The exceptional mode of action produces hypnotic effects and also preserves normal sleep pattern along with decreased possibility of cataplexy [187]. In the phase II clinical studies, the drug was found to enhance sleep initiation and prolonged sleeping time. The drug is also under investigation for treating hyperarousal-associated insomnia in individuals with depression. Commonly reported adverse effects were dizziness, somnolence, and headache [188–190].

Various patents have been granted/published in this field including solid dosage forms, intranasal solutions, buccal aerosol sprays, and toothpaste, for the treatment of insomnia which are compiled in Table 5.

Table 5. Patents granted/published for various dosage forms for treatment of Insomnia.

Patent no.	Country of filing	Composition/active ingredient	Major outcome	Publication/grant year	Ref.
8926991	USA	Botulinum toxin	For treating primary disorders of mood and affect with a neurotoxin, including depression, nervousness, and sleep disorders.	2015	[191]
US 8252809B2	USA	Zolpidem	Solid dosage form for treating midnight insomnia by administration of low doses (5 mg or less) of zolpidem or a salt thereof.	2012	[192]
US 8242131B2	USA	Zolpidem	Methods and compositions for treatment of midnight insomnia by administration of low doses (5 mg or less) of zolpidem or a salt thereof.	2012	[193]
US 8148393B2	USA	Zolpidem	A modified release zolpidem tablet is designed as a tablet-in-tablet dosage form.	2012	[194]
US 8034371 B2	USA	Zolpidem	Intranasal solutions of zolpidem for the prevention/treatment of insomnia or the therapy of neurological diseases.	2011	[195]
US 7914826	USA	Combination containing melatonin and other herbal supplements	Supplemental compositions and methods for inducing a restful night's sleep by rapidly inducing a person to fall asleep and to maintain sleep.	2011	[196]
US 7906154	USA	Combination containing melatonin and other	Supplemental compositions and methods for inducing a restful night's sleep by rapidly inducing a person to	2011	[197]

10. Conclusion

Insomnia is a typical and frequently crippling disease and is known to have remarkable adverse outcomes for physical health and well-being. For the treatment of this condition, fortunately, both behavioural and pharmacological therapies are available. Various treatments have been reviewed in this article to provide a resource for physicians, with the expectation that this would enhance the clinical management of insomnia. Currently, there is little customization of the most often utilized hypnotics depending on individual insomnia symptoms and comorbidities. Choice of therapy depending on the patient's particular symptoms and clinical either with dose titrations or by utilizing combination of drugs (within or outside the DORA class) may provide a type of customized insomnia treatment that until now has not been underlined. Significantly, since drugs in this category appears to have less addiction and minor rebound insomnia, the DORAS can be interestingly combined with CBT-I, which is generally viewed as an effective and enduring non pharmacological therapy for both primary and comorbid insomnia. With wide availability of novel modalities for CBT-I, like individual and group teletherapy, via web-based applications, and others, the role of customizable, titratable hypnotics might be exceptionally complementary. Nowadays when personalized clinical treatment is turning out to be progressively realistic, such advances may assist in keeping insomnia to bed.

Conflicts of Interest

The authors report no conflicts of interest.

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Original Article

Exploration of Inbuilt Novel Properties as Bioretardant Cum Stabilizer of Isolated Biopolymer from *Fragaria ananassa* in Delivery of Nanosized Phenytoin

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Abstract

The research aims to develop bionanosuspension using a biopolymer isolated from *Fragaria ananassa* fruit that constitutes potential and natural polymeric properties. At first, the biomaterial was isolated from the natural fruit pulp of *Fragaria ananassa* by an economical method of isolation. The model drug was nanosized by a novel sonication method. The isolated biopolymer was characterized for its polymeric properties, and its potential capabilities were evaluated in the delivery of nanosized phenytoin. The isolated biopolymer was characterized for DSC, FTIR, NMR, mass, and scanning electron microscopy. The isolated biomaterial was used for the preparation of phenytoin-loaded bionanosuspension with other excipients. The bionanoparticles were also characterized by different analytical testing such as FTIR, DSC, and SEM to confirm any interaction between model drug and biopolymer.

The prepared bionanoparticles showed the release of phenytoin in a sustained manner over 36 hours. The release kinetic study was done using the BIT-SOFT 1.12 software and other parameters such as t50%, t80%, and r^2 were calculated. The formulation PFr6 was considered best having t50% in 18.22 hours and t80% in 29.62 h with an r^2 value of 0.9793. This formulation showed up to 87.89% drug release within 36 hours. The prepared bio-nanosuspension was found to be stable and in a well-dispersed state. The dried bionanosuspension evaluation revealed no interaction between model drug and biopolymer without any loss of characteristic peaks. Therefore, the isolated biopolymer can be safely used to prepare stable bionanosuspension loaded with nanosized phenytoin.

Keywords: Biopolymer; Bionanoparticles; Bionanosuspension; Epilepsy; *Fragaria ananassa*, nanosizing; Phenytoin

Introduction

Polymers are the first choice for designing novel drug-delivery systems for sustained release, controlled release, extended release, and targeted drug-delivery systems (1).

Nowadays, researchers have proved that biopolymers are one of the most novel and intelligent biomaterials isolated from various natural sources such as bark, seeds, flowers, fruits pulps, leaves, and other natural sources (2). These biopolymers have good film-forming, mucoadhesivity, sustainability, retardability, release rate, and controlling ability. These can be used to design novel drug-delivery and targeted drug-delivery

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systems (3–5).

In this research work, bionanosuspension with bionanoparticles loaded with nanosized phenytoin has been prepared using the novel biomaterial (7) from fruit pulp of *Fragaria ananassa*. For developing bionanoparticles and their suitability for the release of phenytoin, the potentiality of biopolymers was evaluated.

Epilepsy is a very common neurological disorder of the brain. In epilepsy, the brain does not normally act that results in seizures or episodes of abnormal behavior, sensations and may sometimes lead to loss of awareness (6). Phenytoin is an antiepileptic drug available in the form of tablets, capsules, and an oral suspension. By designing the antiepileptic drug-loaded bionanosuspension for targeting to brain via ear, the challenges in treatment of epilepsy on oral or other rote administration can be conquered easily, that too in an efficient way (7).

Zhou et al. researched liposomes coated with phenytoin prepared by thin-film dispersion method (8). These prepared liposomes were partially inhibitors of I/R injury and reduced the infarct size and left ventricular fibrosis after I.V. administration. Fuller *et al.* described the comparison of tolerability, safety measures, and different side effects of levetiracetam and phenytoin after intravenous administration (9). So in a regimen of epilepsy, no significant difference was observed between levetiracetam and phenytoin after intravenous plus oral regimen. Wang *et al.* developed electroresponsive hydrogen nanoparticles for the delivery of phenytoin in the brain (10). Phenytoin was distributed significantly to brain tissues and during tonic-clonic seizures. It was released in significant concentration for the treatment of seizures. Baumgartner *et al.* designed phenytoin-loaded nanosuspension (11), while Motawea et al. developed phenytoin-loaded nanostructured lipid carriers for topical delivery (12). In another study, Senthilvel *et al.* developed capsules filled with phenytoin- and berberine-loaded nanoparticles to improve anticonvulsant activity (13). In this research, biopolymer was isolated from the natural fruit pulp of *Fragaria ananassa* because of its excellent nutritional properties such as consistency in the rich amount of proteins, vitamins, and minerals (14), several industrial applications for the preparation of jam, jelly, and squash. It is also used in the cosmetic industry for preparing different products (15). Biopolymer has excellent film-forming ability and biostability properties (16, 17).

Using the biopolymer, a drug may be delivered in a retardant manner by utilizing its inbuilt bioretardant cum stabilizer properties (17). In this research work, the naturally isolated and characterized biopolymer can be used as an alternative to standard available polymers for targeting CNS for treat disorders associated with brain (18, 19). The drug solubility problems of the drugs can be minimized by converting the drug into its nanosized form (20). Nanosuspension provides an enhanced bioavailability, enhanced uptake by the cells, prolonged duration of action, and avoiding unwanted toxicity systemically (21). By designing the drug-loaded bio-nanosuspension with biopolymer, the solubility problems of the drugs can be solved (22). Mohammadi *et al.* developed whey protein isolated–based biodegradable films incorporated with chitosan nanofiber and cinnamon essential oil. It was concluded that a bio-nanocomposite in packaging technologies at the industrial level is necessary for improving the shelf life of food materials (23).

In this way, this research concludes the isolation of biopolymer from natural source *Fragaria ananassa* and use of isolated biopolymer in developing bionanosuspension for delivery of phenytoin significant as it is the prime need in the treatment of epilepsy for long term. Thus the novel inbuilt properties of isolated biopolymers are not explored yet as a novel drug delivery in pharmaceutical sciences. The biopolymer with novel properties such as bioretardant cum biostabilizer and its isolation at a very economical level can prove a magical key role in designing targeted drug-delivery systems. It can be used as an alternative to existing standard polymers (24).

Experimental

Materials

Phenytoin was obtained as a gift sample from Affy Pharma Private Limited, Baddi.

The *Fragaria ananassa* (strawberry) was purchased from the local market of Lucknow. All other chemicals used were of analytical grades, such as sodium benzoate (Thermo Fischer India Pvt. Ltd), dextrose (Thermo Fischer India Pvt. Ltd), and polyvinyl alcohol (Thermo Fischer India Pvt. Ltd.).

Methods

Isolation of Biopolymer

The *Fragaria ananassa* fruit was purchased from the local market of Lucknow. A volume of 500 g fruit pulp was washed with distilled water. Then it was ground in a grinder till it converted into a paste. A small quantity of distilled water can be added during the grinding, if necessary. This paste was filtered through the muslin cloth. The collected filtrate was centrifuged at 5000 rpm for 10 min (17). After centrifugation, the supernatant was taken. Centrifugation was performed to remove any residue. Then half of the supernatant was treated with methanol in a 1:1 ratio. These were placed in a refrigerator overnight. Then after treatment, these were centrifuged again at 5000 rpm for 30 min. The supernatant was discarded and the biomaterial as sediment was collected and air-dried. If there is any moisture content, it can be dried in desiccators for 48 hours. If the biomaterial (3) consists of any oil, it can be removed by washing with acetone or chloroform. This procedure was repeated and optimized six times, and the yield was calculated. The obtained biomaterial was passed through sieve number 200 and stored for further use (20).

Characterization of Isolated Biopolymer

The physicochemical properties of isolated biopolymer were as follows: color, odor, taste, and solubility. Chemical tests were also performed for the presence of carbohydrates, starch, and proteins. The isolated biopolymer was also characterized based on SEM analysis, DSC testing, IR spectroscopy, mass spectroscopy, and NMR spectroscopy.

Chemical test of isolated biomaterial

Chemical test for carbohydrate

An amount of 1 mL biopolymer solution (5% biopolymer solution in distilled water) was taken in a test tube. Then two drops of Molisch reagent were added, followed by 1–2 mL of addition. Sulfuric acid was poured into the test tube and observed until the purple color appeared at the interface of the two layers formed. The test was performed and reported (25

Test for the presence of protein

For testing the presence of protein, the isolated biomaterial was treated with 0.1% solution of Ninhydrin reagent and 10% tannic acid solution. The presence of blue and yellow color precipitate indicates the presence of protein. The test was performed and reported.

A Biuret test was performed for the confirmation of proteins. A volume of 2 mL biopolymer was taken in a test tube (5% biopolymer solution in distilled water), and 1 ml of sodium hydroxide solution was added along with copper sulfate solution drops. The mixture was kept aside for 5 min, and the color changes were observed. The emergence of violet color confirms the presence of proteins. The test was performed and reported (25).

Spectral analysis of the biomaterials

Spectral analysis such as IR, NMR, mass spectroscopy, and SEM studies of the isolated biopolymer was conducted. The biomaterials were subjected to IR, NMR, mass spectroscopy studies, and the obtained spectra were interpreted and reported. Apart from that, SEM studies of different biomaterials were also performed, and the obtained results were interpreted and reported. IR, NMR, and mass spectroscopy were studied at Central Drug Research Institute Lucknow, and SEM studies were studied at Birbal Sahani Institute of Paleobotany Lucknow (26).

SEM (scanning electron microscopy) analysis

The isolated biopolymer's surface morphologies were characterized by a scanning electron microscope. In SEM analysis, the external surface and internal structure were characterized. The small quantity of biopolymer was taken and fixed on aluminum studs and then coated with gold using the sputter under vacuum atmosphere by a gold sputter module in a high vacuum evaporator. The scanning electron micrograph was taken

for the biopolymer under observation. SEM testing was performed at BSIP, Lucknow using Make, JEOL India Pvt Ltd. Model, JEOL JSM 7610F. The SEM images were interpreted and reported (26).

FTIR spectroscopy of isolated biopolymer

The FTIR spectroscopy was done by preparing the KBr discs. An amount of 1 mg isolated biopolymer was taken and mixed with 100 mg of dried and desiccated solid KBr. The mixture was mixed in mortar and pestle and placed in an IR lamp to remove any moisture. The mixture was converted into a disk under the pressure of 10 tons. The prepared disk was placed in a disk holder in the path of IR radiation. The spectrum was recorded within a range of 4000–200 cm^{-1}. FTIR of hydroxypropyl methylcellulose was also carried out for characterization. The FTIR was done at CDRI, SAIF, Lucknow using Model-Agilent Cary 630 FTIR Spectrometer (range: 4000–450 cm^{-1}). The FTIR spectra were interpreted and reported (26).

Mass spectroscopy

It is a useful and powerful technique for quantifying known materials and identifying unknown materials and elucidating the structure and chemical properties of the molecule. It is an accurate method for determining the molecular mass of the compound. This is performed in a laboratory in which the sample of biopolymers was introduced through the inlet system. The gas-phase ions of the compound were produced. Then with the help of molecular ion fragmentation, the ions were separated in mass spectrometer according to their mass-to-charge ratio. A mass spectrum of ion abundance versus mass-to-charge ratio was recorded, which was done at CDRI-SAIF Department, Lucknow by using Waters PLC-TQD mass spectrometer (ESI-MS, APCI-MS, and LC-MS/MS) and Agilent 6520 Q-TOF (ESI-HRMS and APCI-HRMS). Mass spectra were interpreted and reported (26).

NMR spectral analysis

The NMR spectroscopy was done for spectral analysis of isolated biopolymer. The sample was dissolved in a specific solvent such as $CDCl_3$. The mixture was pumped into the instrument at a high rate of flow. The switch for the valve was used to stop the flow. Then the measurement was performed. After the finishing of measurement, the spectrum was processed and analyzed in an automation computer. This was done at CDRI, SAIF, Lucknow using Advance-400 MHz Bruker, Switzerland. NMR spectra were interpreted and reported (26).

Differential scanning calorimetry testing

DSC testing is the thermal analysis technique in which the heat flow inside or outside of the sample for testing is determined as the function of temperature. Here, the biopolymer sample was taken and exposed to a controlled temperature program. The glass transition temperature was determined. The heat flow range was 30–300 °C. The DSC thermogram was recorded, interpreted, and reported (26).

Nanosizing of phenytoin by sonication method

A volume of 500 mg phenytoin was taken and dissolved in 25 mL methanol. The clear solution was sonicated for 15 cycles continuously. During sonication, 25 mL of purified water was added drop by drop till precipitation was observed. The obtained precipitate was allowed for centrifugation. After each sonication cycle, the sample was allowed for absorbance and %transmittance (%T) and %blockage (100–%transmittance) measurement. The residue was recovered and then dried to collect the nanosized phenytoin in the nanoparticles range. This nanosized phenytoin obtained by this standard solvent evaporation method was evaluated for different parameters. The dried nanosized phenytoin was packed and stored for further use. The phenytoin was also nanosized by a novel sonication method. Here 500 mg of phenytoin was taken and mixed with dextrose and 25 mL double distilled water. This dispersed solution was sonicated for 15 cycles continuously. During sonication, 25 mL of purified water was added drop by drop till precipitation was observed (17). The obtained precipitate was allowed for centrifugation. After each sonication cycle, the sample was allowed for absorbance and transmittance%

(T%) and blockage% (100–transmittance%) measurement. The residue was recovered and then dried to collect the nanosized free-flowing phenytoin powder. The procedure was repeated in triplicate.

Drug–Excipient Interaction Study

The drug–biopolymer interaction study was performed by the UV spectroscopy method. The phenytoin–biopolymer mixture was prepared in a ratio of 1:1, 1:3, and 3:1 by wet and dry mixing. After mixing, the drug and polymer mixture was preserved at a temperature of 50 °C for 3 days in the wet method and then diluted with solvent and scanned for the absorption maxima (λ_{max}). In the dry method, three different ratios of drug–biopolymer were prepared in their physical form. Then after storing at room temperature, this was diluted with 2 mL of methanol and then scanned by UV spectrophotometer for any change in λ_{max}.

Formulation of Phenytoin-Loaded Bionanosuspension

The formulations of bionanosuspension were prepared using the different drug–biopolymer ratios, as shown in Table 1. The bionanosuspension was prepared by sonication of the mixture of drug and biopolymer and other excipients such as polyvinyl alcohol as a suspending agent, sodium benzoate as the preservative, purified water, and dextrose as nanosizent. The phenytoin, Fragaria × ananassa biopolymer, and other excipients were accurately weighed and triturated with double-distilled water. This mixture was sonicated for 3 cycles. Then 0.5 mL of polyvinyl alcohol (0.5%) was added during sonication. The volume was made up to 10 mL with double-distilled water having sodium benzoate content of 0.1–0.5%. Dextrose can be added if necessary as a nanosizing agent and allowed for sonication for 15 cycles. After sonication, the bionanosuspension was refrigerated for 2 days. If there is no settlement, then it can be considered that the formulation is optimized, but if having a settlement, then the abovementioned amount of polyvinyl alcohol was again added and allowed for sonication for 10 cycles and refrigerated for 48 h. Different formulations were prepared, and after optimization according to stability, the formulations PFr1–PFr6 were prepared. After formulation, their stability was tested and then evaluated for different parameters, including release study (20).

Characterization of phenytoin-loaded bionanosuspension

Dispersibility study of bionanosuspension

A volume of 10 mL formulated bionanosuspension was taken and dispersed in 20 mL of the distilled water in a test tube. The time for settling of the dispersed nanoparticles in the bottom was noted, and then again, the nanoparticles were redispersed and noticed for the redispersion. After shaking, any lump or aggregates or any precipitation formation was observed (20). The procedure was repeated in triplicate.

pH study of bionanosuspension

The pH of formulated bionanosuspension was evaluated with a digital pH meter. The study was done in triplicate, and the mean was taken and checked which helps determine if the pH of the nanosuspension is within the required range. The procedure was repeated in triplicate (20).

Entrapment% efficacy of loaded bionanosuspension

The freshly formulated bionanosuspension was taken and centrifuged at 5000 rpm in

Table 1. Formulation table of phenytoin-loaded bionanosuspension using *Fragaria ananassa* biopolymer.

Formulations	PFr1	PFr2	PFr3	PFr4	PFr5	PFr6
Drug:biopolymer ratio	1:4	1:5	1:8	1:10	1:12	1:15
Phenytoin (mg)	10	10	10	10	10	10
Fragaria ananassa Biopolymer (mg)	40	50	80	100	120	150
Polyvinyl alcohol (mL)	0.5	0.5	0.5	0.5	0.5	0.5
Sodium benzoate (%)	0.5	0.5	0.5	0.5	0.5	0.5
Double-distilled water (mL)	10	10	10	10	10	10

an ultracentrifuge. After centrifugation, the supernatant was taken and diluted up to 10 µg/mL, and the amount of drug unincorporated was measured by determining the absorbance under UV spectroscopy at 216 nm. The amount of the drug loaded in the nanoparticles was calculated by subtracting the amount of free drug in supernatant from the initial amount of drug taken in the formulation. The procedure was repeated in triplicate (22). This determination was done in triplicate, and the average was calculated by using the following formula:

$$\text{Entrapment efficacy\%} = \frac{\text{Amount of drug loaded in nanoparticles}}{\text{Initial amount of drug taken in formulation}} \times 100$$

Particle size screening of the nanoparticles in bionanosuspension by UV method

The bionanosuspension was evaluated by measuring the percent transmittance of the bionanosuspension. The percent transmittance was measured as a function of the particle size in nanorange done by the sonication method. The % transmittance depends on the particle size range within a particular range that defines the size of the particles below or beyond the size range required. The transmittance% was determined before and after the sonication cycle. The transmittance% at different wavelengths indicates that when the light passes through the particles, it indicates that the particle size is below that wavelength which shows that the percentage of the particles is less than 400 nm in the mixture and the blockade% shows that the percentage of particles is more than that. The transmittance% was measured by using the UV spectrophotometer. After each sonication cycle, it was increased due to the reduction of the particles to nanorange. The effect of sonication on %transmittance was observed after sonication and measuring after each sonication cycle (22). The procedure was repeated in triplicate.

Particle Size Analysis

The particle size of the bionanosuspension was studied by characterizing with the Malvern Zetasizer. The particle size distribution by intensity was confirmed by using the zetasizer (22).

In-vitro release study of bionanosuspension

The in-vitro release study was performed for all formulations. *In-vitro* release study was performed by a novel static method by using modified M.S. Diffusion apparatus. It consists of two compartments: one for the donor and the other for the receiver. The formulation for the release study was taken in the donor compartment (1 mL) and the end of the donor is tied with the egg biomembrane. This donor compartment was immersed in the receiver compartment having 13 mL of pH 7.4 phosphate buffer solution. Sampling was done at different regular time intervals for 36 h. The samples were withdrawn completely and replaced with the fresh phosphate buffer solutions after every sampling. The samples were analyzed by UV spectrophotometer for determining the released amount of the drug. The graph was plotted between the CDR% and time. Other parameters such as r^2, t50, and t80% were calculated to evaluate release study from different formulations and the selection of the best formulation (22).

Stability Study

The stability study was performed as per ICH guidelines. The formulated bionanosuspension was stored for 6 months at different ambient temperatures. The bionanosuspension was kept at two different conditions at 25 °C ± 2 °C, 60% RH and 40 °C ± 2 °C, 75% RH stability chamber. The samples were observed every 2 weeks for their different parameters during the testing period. The samples under evaluation were observed for the drug content, pH changes, any changes in color, appearance, entrapment efficacy (22).

Results and Discussion

Isolation of Biopolymer

The *Fragaria ananassa* biopolymer was found to be white with a yield% of 13 ± 2. The color-changing point was found to be 229 °C ± 5 °C.

Characterization of Isolated Biopolymer of Fragaria ananassa

The isolated biopolymer was white color in appearance. The biopolymer was found to be odorless with a characteristic taste. It

was found to be sparingly soluble in water. It showed a positive test for carbohydrate and protein (20). The characterization of isolated biopolymer of *Fragaria ananassa* is shown in Table 2.

SEM analysis of biopolymer

The isolated biopolymer was analyzed by scanning electron microscopy for surface characterization. The SEM analysis shows the rough and flaky structure of the biopolymer. The granular structure was also observed in the SEM image. This confirms the polymeric nature of the biopolymer having a flaky and granular structure (22). The SEM image of isolated biopolymer is shown in Figure 1.

Different Spectral Analysis and Their Findings

IR spectral analysis of isolated biopolymer

FTIR spectra of the isolated biopolymer show the presence of different functional groups responsible for the polymeric nature of the isolated biopolymer. The IR spectra show the presence of different functional groups such as hydroxyl (3396.15 cm^{-1}), alkynes (669.43 cm^{-1}), and carboxylic acid (1410.35 cm^{-1}), which confirms its polymeric characteristics. Other groups such as amide at 1639.02 cm^{-1}, alkane at 2925.45 cm^{-1}, tertiary alcohol at 1215.89 cm^{-1} were present in the IR spectra. The presence of these functional groups is responsible for the retardibility in drug release like other standard polymers (22). FTIR spectra are shown in Figure 2.

Table 2. Characterization of isolated biopolymer of *Fragaria ananassa.*

Parameters evaluated	Observation
Color	White
Odor	Characteristic
Taste	Characteristic
Melting Point	229 °C ± 5 °C
Solubility	Soluble in water, soluble in methanol
Carbohydrate	Present
Protein	Present

Differential scanning calorimetry (DSC) study of isolated biopolymer

The DSC thermogram of *Fragaria ananassa* shows peaks at 83.794 Celsius, 161.035 Celsius, and 208.709 Celcius. The area was found to be 229 mJ/mg, 30.5 mJ/mg, and 10.3 mJ/mg, respectively. The thermogram showed the sharp endothermic broad peak that deals with the amorphous nature of biopolymer (Figure 3).

Mass spectroscopy of isolated biopolymer

Mass spectra reveal that the isolated biopolymer is polymeric due to the presence

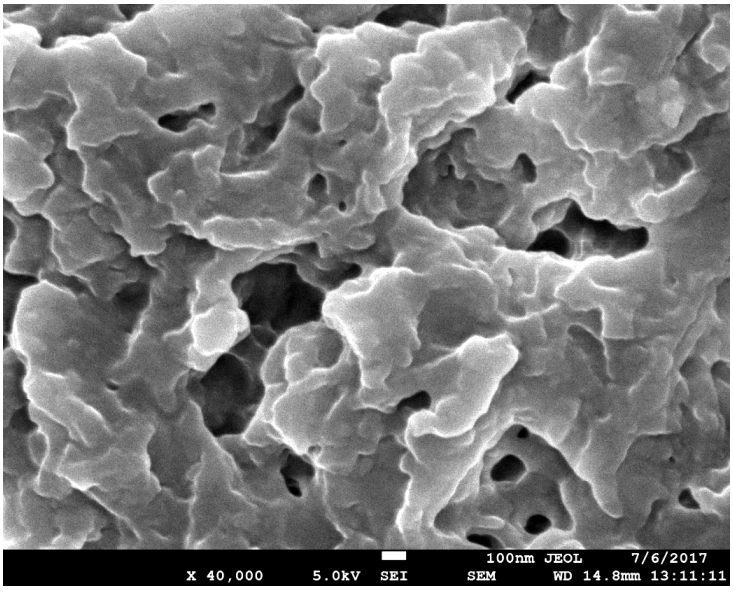


Figure 1. SEM of isolated biopolymer from *Fragaria ananassa* at 40,000×.

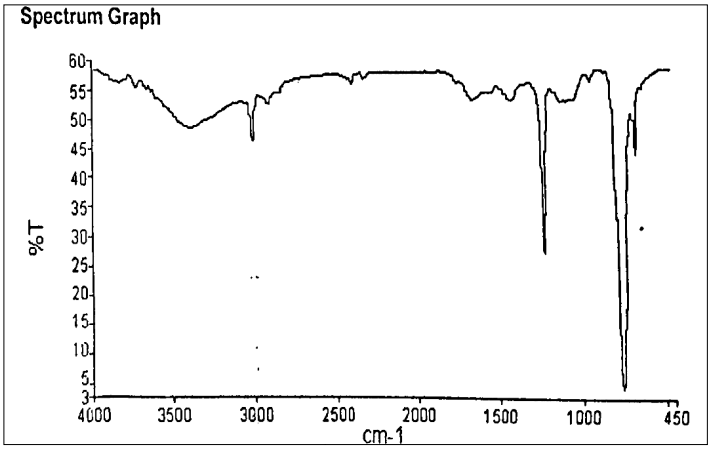


Figure 2. FTIR spectra of biopolymer from *Fragaria ananassa*.

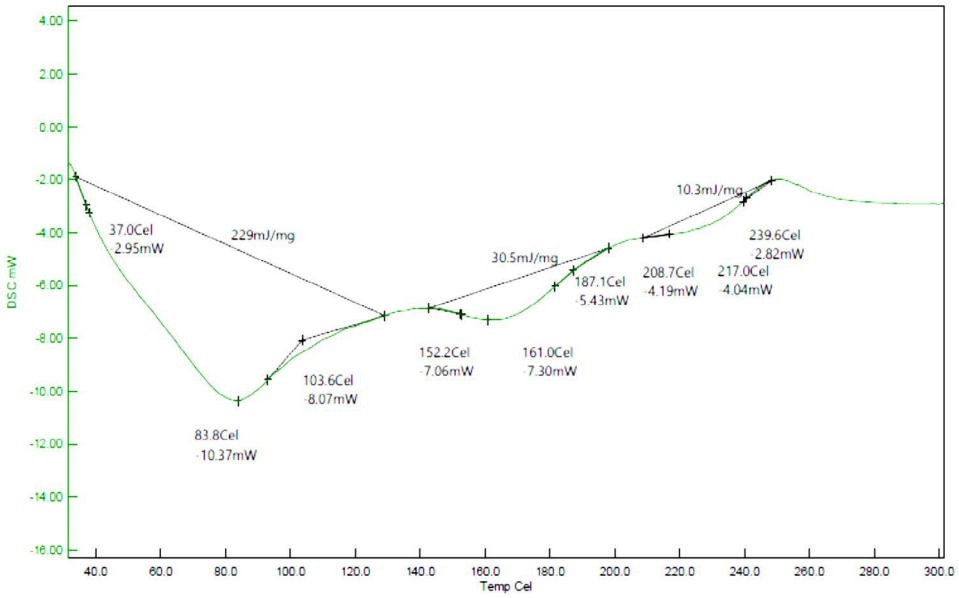


Figure 3. DSC of biopolymer from *Fragaria ananassa*.

of large molecular weight structures. It indicates the presence of protein. HRMS spectra of isolated biopolymer showed the parent peak at m/z 456.33, confirming its large molecular weight structure such as a polymer (27) (Figure 4).

NMR spectroscopy of isolated biopolymer

The NMR spectra show the presence of different peaks such as multiplet at 0.829–0.902 ppm which reveals the presence of primary alkyl group; peaks at 1.232 ppm confirm the presence of methylene group and at 1.255 ppm the presence of hydroxyl group. This presence confirms its polymeric nature (27) (Figure 5).

Nanosizing of phenytoin

During the nanosizing of phenytoin after each sonication cycle, the sample was observed for measurement of percent transmittance which confirmed that when the number of sonication cycle was increased, the percent transmittance was also found to be increased. This was due to a decrease in particle size and particles are now are in

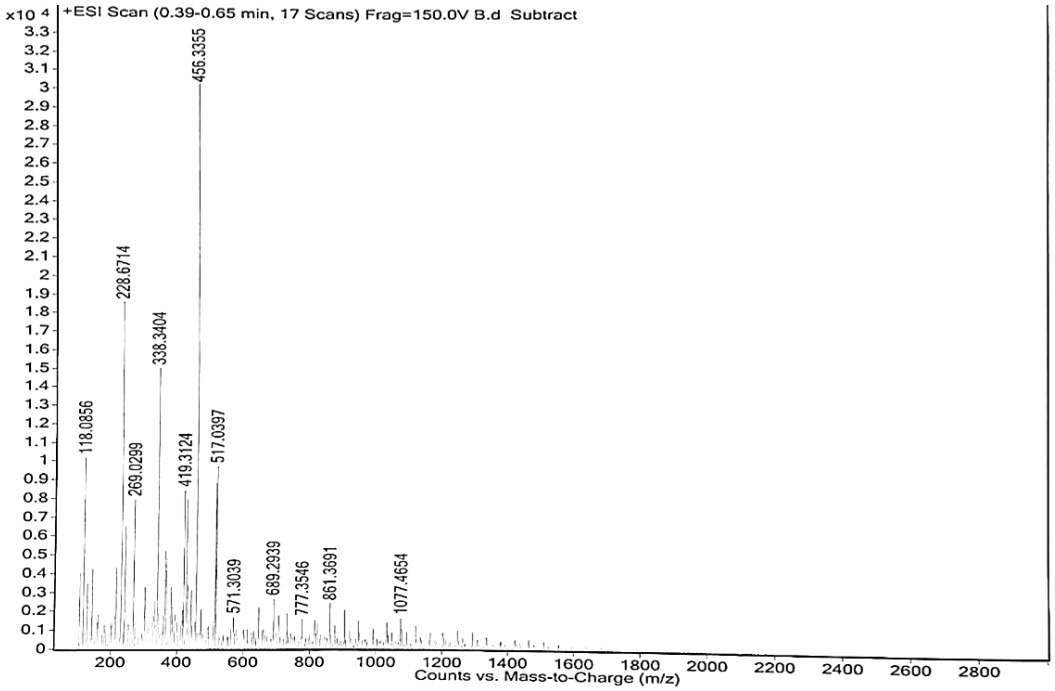


Figure 4. High-resolution mass spectrum of isolated biopolymer from *Fragaria ananassa*.

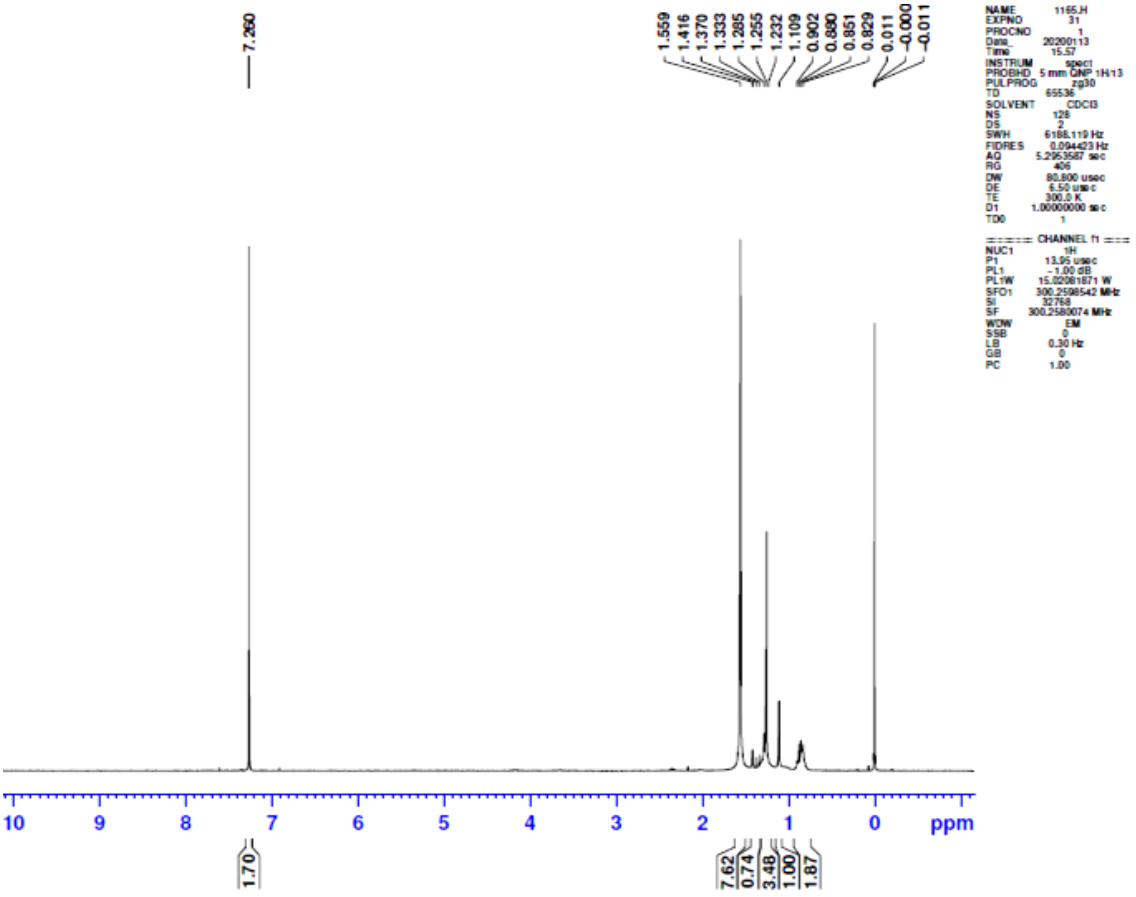


Figure 5. NMR spectra of biopolymer from Fragaria × ananassa.

nanorange. Thus, transmittance percent shows that the percentage of particles less than 400 nm in bionanosuspension and blockadepercent gives an idea about the percentage of particles which is above 400 nm. Thus the UV method has given an idea about particles in nanorange (22).

Drug-Excipient Interaction Study

No change was noticed in λ_{max} before (216 nm) and after the test (216 nm) in the drug-excipient study. The absorption maxima of phenytoin *Fragaria ananassa* mixture was closed to the λ_{max} of pure drug. There was no significant change in λ_{max} of drug–polymer mixture as compared to pure drug. It means that it confirms no interaction between drug and biopolymer and other excipients too. It was observed that excipients are not interacting and not producing any changes in drug properties so that the isolated biopolymer can be used to prepare bionanosuspension (27).

Formulation of Phenytoin-Loaded Bionanosuspension

Different formulations of bionanoparticles by using different ratios of biopolymer from *Fragaria ananassa* and phenytoin were prepared. Then post formulation of bionanosuspension was evaluated for different parameters and their finding are described below.

Dispersibility Study of Bionanosuspension

The dispersibility of the formulated bionanoparticles was found to be excellent, and the redispersion was also found to be good. All nanoparticles were in a dispersed state during dispersion (20). No aggregation or lump formation was observed (Table 3).

pH study of Bionanosuspension

The pH of the bionanosuspension was found to be in the range of 7.3 ± 0.22 to 7.7 ± 0.19. It means that the formulations were in desired pH range that is suitable for the stability of the bionanosuspension (20). The pH of the different bionanosuspension formulations observed is given in Table 3.

%Entrapment efficacy of loaded bionanoparticles

The entrapment efficacy of the formulated bionanosuspension was found in the range of 84.56 ± 2 to 88.02 ± 1.8%. Thus the formulated bionanosuspension PFr6 showed the maximum entrapment efficacy up to 88.02 ± 1.8% (Table 3).

Transmittance% of Bionanosuspension

Transmittance% was found to be in the range of 91 ± 1.2% to 98 ± 0.75% after 15 cycles of sonication. Here, the UV method was used for screening the size of bionanoparticles in bionanosuspension. It was observed that as the sonication cycle was increased, the %transmittance was found to be increased because the particle size after sonication has come in nanorange. The transmittance% indicated the percentage of particles below 400 nm, and the blockade% showed the percentage of particles above 400 nm when screened by the UV spectrophotometry method. Thus, the UV method can be used as a screening method to determine nanoparticles' size in bionanosuspension (20).

Particle size analysis

The nanoparticles size in bionanosuspension (PFr6) was 238.5 nm after evaluating with Malvern Zetasizer. Thus, the obtained size with the zeta potential of –20.1 mV confirms that the nanoparticles are in nanorange, which is responsible for the stability of nanosuspension. It also confirms that the stable bionanosuspension loaded with phenytoin was prepared using smart isolated *Fragaria*

Table 3. Different formulations with observed pH, dispersibility, entrapment% efficacy values.

Formulations	Observed pH	Dispersibility	Entrapment efficacy (%)
PFr1	7.4 ± 0.32	+	84.56 ± 2.0
PFr2	7.3 ± 0.22	+	86.16 ± 2.8
PFr3	7.5 ± 0.11	+	85.16 ± 1.6
PFr4	7.7 ± 0.19	+	86.20 ± .88
PFr5	7.4 ± 0.12	+	87.02 ± 1.8
PFr6	7.5 ± 0.05	+	88.02 ± 1.8

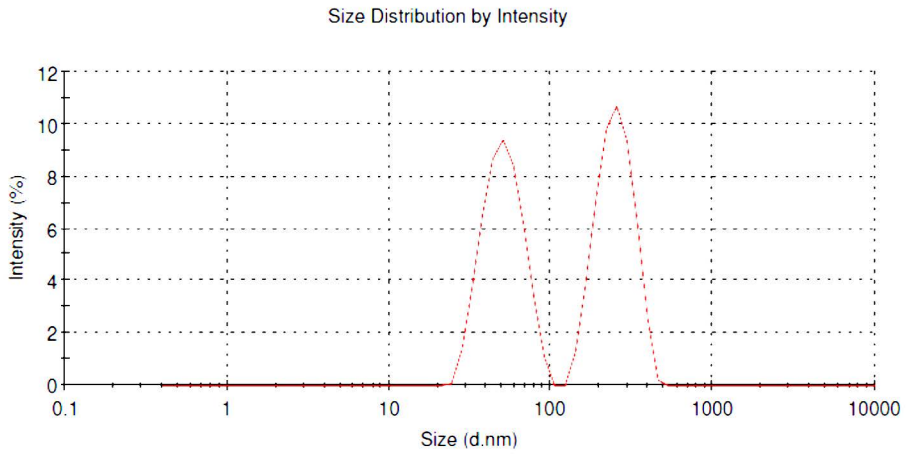
ananassa biopolymers. The result reveals that it can be safely used for delivering the phenytoin from the prepared bionanoparticles in the treatment of epilepsy (20). The particle size distribution in bionanosuspension is shown in Figures 6a and 6b.

FTIR of bionanoparticles and phenytoin-loaded bionanoparticles

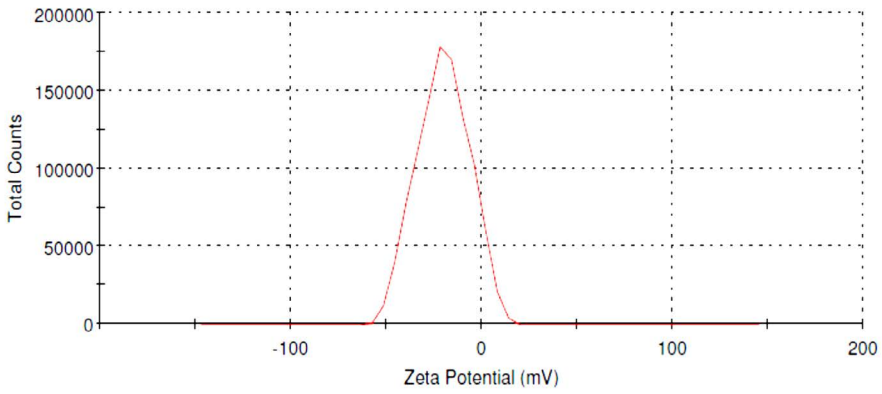
The FTIR spectroscopy of the dried phenytoin-loaded bionanoparticles revealed no interaction between the model drug and the biopolymer used. The appearance of a new peak or disappearance of the existing peaks was not observed in this spectroscopy. The results indicated that there was no loss of the functional peaks of drug having C–H stretching, C–H bending, C–O stretching, and O–H stretching with isolated biopolymers with much-closed peak values as that of the pure drug, whereas FTIR of bionanoparticles suggested the biopolymeric nature of bionanoparticles with the presence of characteristic peaks very similar to the peaks as observed in FTIR of biopolymer at 669 (C–H bending), 1215.93 (C–O stretching), 3021.27 (C–H stretching) and 3264.99 cm^{-1} (O–H stretching). The obtained spectra of bionanoparticles and phenytoin-loaded bionanoparticles are shown in Figures 7A and 7B.

Differential scanning calorimetry of bionanoparticles and phenytoin-loaded bionanoparticles

The DSC of bionanoparticles showed the biopolymeric nature with a broad endothermic peak at 72.4 °C. The DSC thermogram of



(a)



(b)

Figure 6. (a) Particle size distribution in bionanosuspension and (b) zeta potential.

phenytoin-loaded bionanoparticles revealed its crystallinity. These also showed a sharp endothermic peak at 135.2 °C which indicated the presence of a small and wide endothermic peak, further showing that the crystalline drug was converted in partially amorphous form during the nanosuspension formulation and nanosizing. There was also a shift of melting peak to the lower temperature in formulated bionanoparticles which was due to the conversion of phenytoin crystal form in nanorange during sonication. The obtained DSC thermogram of bionanoparticles and phenytoin-loaded bionanoparticles is shown in Figures 7C and 7D.

Zeta particles size of bionanoparticles and phenytoin-loaded bionanoparticles

The zeta particle size of bionanoparticles and phenytoin-loaded bionanoparticles analysis revealed that the bionanoparticles were found to be 136.1 nm and its size was found to be 147.7 nm (refer to Figures 7E and 7F). The bionanoparticles and phenytoin-loaded bionanoparticles zeta particle sizes were suitable for an easy target to the desired site.

SEM of phenytoin-loaded bionanoparticles

The scanning electron microscopy of phenytoin-loaded bionanoparticles showed a

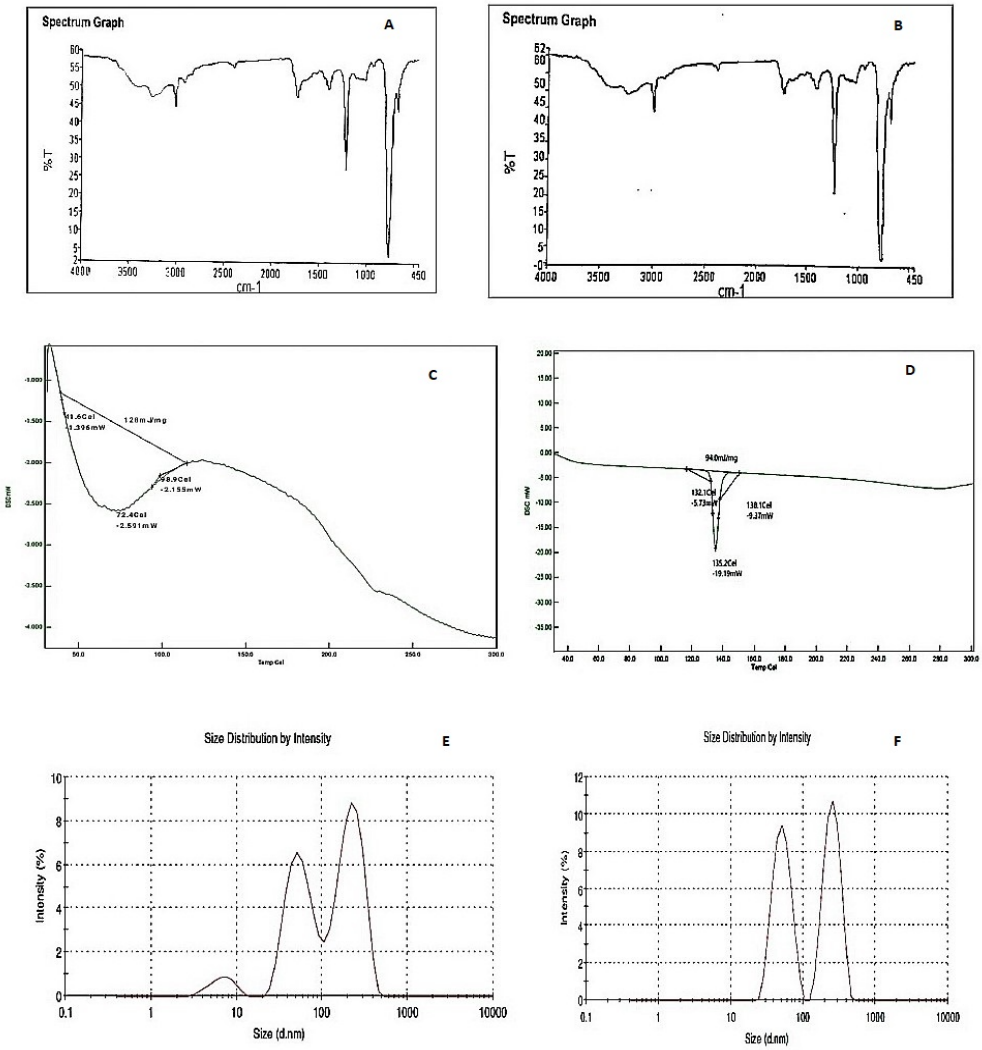


Figure 7. A. FTIR of bionanoparticles B. FTIR OF Phenytoin loaded bionanoparticles C. DSC of bionanoparticles D. DSC of Phenytoin loaded bionanoparticles E. 136.1 nm size of bionanoparticles F. 147.7 nm size of Phenytoin loaded bionanoparticles.

more regular uniform shape with more or less rough surfaces. The aggregates were observed, which may result from the aggregation of some individual bionanoparticles because of the reveal of water or any moisture during the drying of bionanosuspension in the form of dried bionanoparticles. This more or less rough surface may be attributed to the adsorption and biopolymer coating of the model drug. SEM of phenytoin and bionanoparticles is shown in Figure 8.

In-vitro release study of bionanosuspension

The in-vitro release study was done using the M.S. Diffusion apparatus. The release kinetic study was done using the BIT-SOFT 1.12 software and other parameters such as t50%, t80%, and r^2 were calculated. All the formulations showed more than 87.89% drug release (Figure 9). The *in-vitro* release study of different formulations showed the drug% release from 87.89 to 93.26. The different formulations were evaluated for the *in-vitro* release study and release kinetic was studied. The formulation PFr6 was the best formulation with t50% of 18.22 hours and t80% of 29.62 h with a r^2 value of 0.9793. The best formulation -PFr6- showed up to 87.89% drug release in 36 hours. According to the release kinetic study, the best fit model was found to be Korsmeyer–Peppas and the mechanism of drug release was found to be

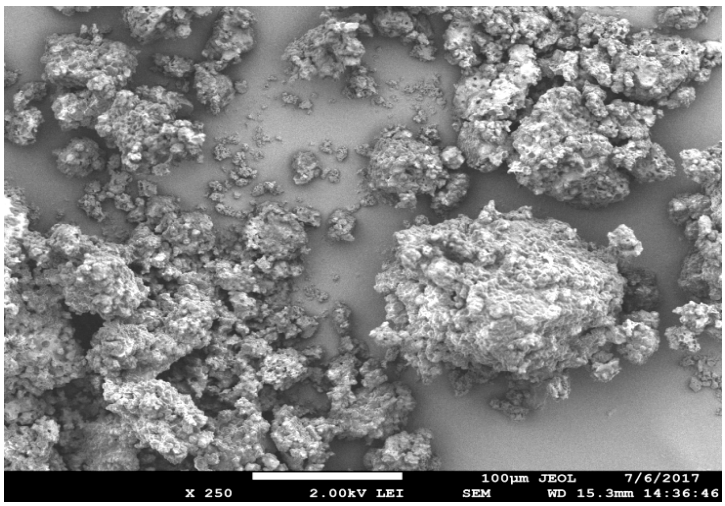


Figure 8. SEM of phenytoin-loaded bionanoparticles.

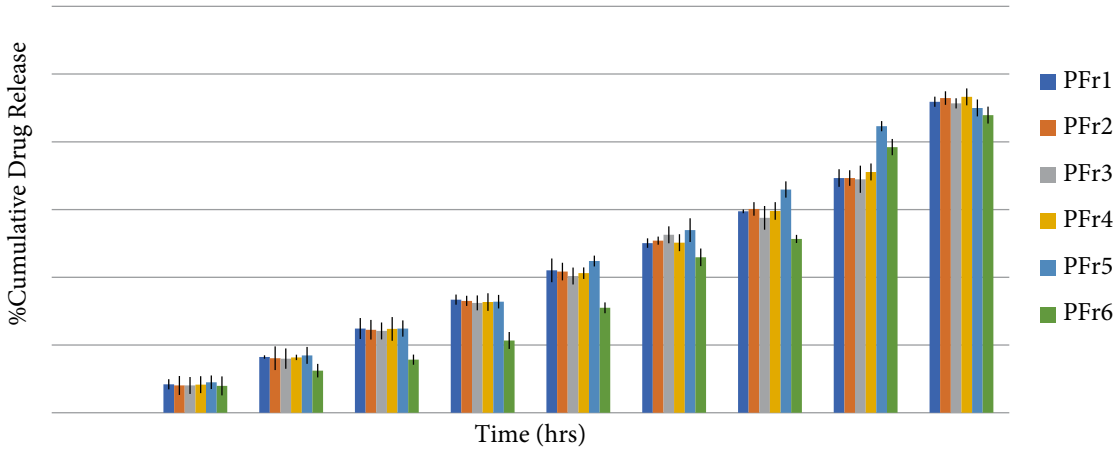


Figure 9. *In-vitro* release drug profile of different bionanosuspension formulations (PFr1–PFr6). The results are expressed as mean ± SD (n = 3).

anomalous transport. The result obtained from the *in-vitro* release study and analysis of the release kinetic of all formulations indicates the sustained release of the phenytoin from the bionanosuspension (22).

Stability Study

The optimized formulations showed no change in λ_{max}, entrapment efficacy and drug release. So there was no drug loss during the study period. The other evaluation parameters also showed satisfactory result. The best-optimized formulation was found to be stable over 6 months. There was no change in color, odor, pH, and physical appearance. During the stability study period, the results obtained were satisfactory from different parameters and the formulation PFr6 was found to be the best optimized stable formulation. The obtained results from the study confirmed that the formulation was physically and chemically stable (22).

The biopolymer is a novel biomaterial with many in-built properties that may be used for delivering drugs to the target. The isolated biopolymer may be used to prepare a novel and intelligent carrier system for loading phenytoin for the treatment of epilepsy. The bionanoparticles are the nanorange particulate systems that may efficiently deliver antiepileptic drugs such as phenytoin.

In this research work, phenytoin was nanosized by a novel and standard method. The biopolymer was isolated from the fruit of *Fragaria ananassa* with good polymeric properties. It can be suitably used for the preparation of bionanoparticles in the form of bionanosuspension. The isolated biopolymers showed good entrapment efficacy. This biopolymer has novel in-built properties such as filmability, retardability, and release rate controlling capability. It may be used for preparing suitable bionanosuspension for delivering nanosized phenytoin. In-vitro release and release kinetic study reveal that the isolated *Fragaria ananassa* biopolymer consists of the desired bioretardant and biostabilizer novel properties. The nanosized phenytoin particle size was screened by the UV method that gave an idea about the particle size range. This method may be used to screen of the nanosize range of phenytoin as well as prepared bionanosuspension (22).

The obtained results reveal that the isolated biopolymer consists of promising polymeric properties that can be used as a bioretardant cum stabilizer to prepare stabilized bionanosuspension. The spectral characterization reveals its polymeric nature (27).

The pH, dispersibility, and entrapment efficiency were found to be significant. The nanosizing of the drug showed satisfactory results for entrapment as well as in overcoming the solubility problem of phenytoin (20).

The particle size of the formulated bionanosuspension was evaluated by measuring the %transmittance as well as with the help of measuring zeta particle size and zeta potential (22).

The transmittance% measurement revealed that the prepared bionanosuspension has a satisfactory particle size in nanorange that is responsible for its stability. The particle size for the zetasizer was 238.5 nm, confirming its nanoparticle size range for the best formulation PFr6. The stability of bionanosuspension was also showed significant with –20.1 mV zeta potential. This means that the particles are in a well-dispersed state without any agglomeration with good repulsive force (22).

Thus, bionanosuspension (PFr6) prepared using the biopolymer from *Fragaria ananassa* showed a significant entrapment efficacy and sustained release of phenytoin for more than 36 hours. So biopolymer from *Fragaria ananassa* can be safely used for the formulation of stable bionanosuspension (29, 30). The isolated *Fragaria ananassa* biopolymer was novel, nontoxic, nonreactive, biocompatible, inert, and biodegradable. So the biopolymer can be safely used as the novel biomaterial in delivering nanosized phenytoin (31). It can be safely used as an alternative to synthetic and semisynthetic available polymers for delivering phenytoin in the treatment of epilepsy.

The phenytoin-loaded bionanosuspension was converted into dried bionanosuspension. The dried bionanoparticles evaluated by different instrumental techniques revealed no loss of functional groups during the preparation of bionanosuspension. The biopolymer was found to be compatible with the drug. The

evaluation findings revealed that *Fragaria ananassa* could be safely used to isolate of biopolymer and its utilization in preparation phenytoin-loaded stable bionanosuspension. The stability of bionanosuspension as well as bionanoparticles, is attributed to its inbuilt biostabilizing property. The release of drug from bionanoparticles revealed that biopolymer could also be safely used to develop bionanoparticles for the release of model drug in a sustained manner for a prolonged time, which is the prime need for long-term treatment of epilepsy. Thus, biopolymer isolated from *Fragaria ananassa* can be safely used in developing novel bionanosuspension.

Conclusion

This research work concludes that the isolated biopolymer from *Fragaria ananassa* fruit serves as a potential, natural polymeric nature biomaterial that can be used for preparing nanosized phenytoin-loaded bionanoparticles in the form of bionanosuspension. The best formulation PFr6 prepared using this natural and biodegradable isolated biopolymer from the edible natural fruit pulp was stable. It releases a significant amount of nanosized phenytoin for the treatment of epilepsy (32). So it was concluded that the isolated biopolymer from *Fragaria ananassa* fruit might be safely used as the novel biomaterial in delivering nanosized phenytoin from the formulated bionanoparticles significantly for an extended time (33).

Acknowledgements

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Research Article

Topical Delivery of Geranium/Calendula Essential Oil-Entrapped Ethanolic Lipid Vesicular Cream to Combat Skin Aging

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The present study deals with the evaluation of the age-defying potential of topical cream formulations bearing Geranium essential oil/Calendula essential oil-entrapped ethanolic lipid vesicles (ELVs). Two types of cream formulations were prepared, viz., conventional and ELVs spiked o/w creams. Essential oil- (EO-) loaded ELVs were characterized by vesicle size, polydispersity index, encapsulation efficiency, and scanning electron microscopy. The cream formulations were evaluated for homogeneity, spreadability, viscosity, pH, *in vitro* antioxidant capacity, sun protection factor, and *in vitro* collagenase and elastase inhibition capacity. Confocal laser scanning microscopy (CLSM) was performed to ascertain skin permeation of conventional and vesicular cream. The results of *in vitro* antioxidant studies showed that GEO-/CEO-loaded vesicular creams have notable antioxidant capacity when compared to nonvesicular creams. GEO- or CEO-loaded vesicular creams exhibited the highest SPF value 10.26 and 18.54, respectively. Both the EO-based vesicular creams showed *in vitro* collagenase and elastase enzyme inhibition capacity. CLSM images clearly depicted that vesicular cream deep into the skin layers. From the research findings, the age-defying potential and photoprotective effects of GEO and CEO were confirmed. It can be concluded that ELVs are able to preserve the efficiency of EOs and have the potential to combat skin aging.

1. Introduction

Finding solutions against various signs of skin aging has been a natural human desire for centuries. Skin aging is a complex biological process, influenced by a combination of intrinsic (genetics, cellular metabolism, hormone, and metabolic processes) and extrinsic factors (chronic light exposure, pollution, ionizing radiation, chemicals, and toxins) [1]. These triggers cause the skin to deteriorate over a timeframe, affecting the wellbeing, wellness, and physical appearance of a person. Because of the fact that skin health and beauty are considered among the principal factors representing overall well-being in humans, age-defying cosmetic product market is observed to be one of the rising markets in today's world. Age-defying cosmetics can act efficaciously when they reach their target sites present in the deeper layers of the skin, but the stratum corneum is the biggest obstacle in delivering the actives deep into the skin layers. Several antiaging strategies have been developed during the past years to overcome this barrier. One of the possibilities for increasing the penetration of active ingredients is the use of vesicular delivery systems such as liposomes, niosomes, and ethosomes [2]. These vesicles can act either as a carrier system or as penetration enhancers. Lipid vesicles indicate their potential as carriers of cosmetics for plant extracts, phytochemicals, and other active ingredients which are poorly soluble, poorly absorbed, and unstable constituents. Lipid vesicles have shown tremendous potential to improve the effectiveness and efficiency of the delivery of cosmeceuticals and bioactive compounds [3]. Conventional liposomes,

on the other hand, appear to be limited to the upper layers of the skin and act as a local reservoir for active ingredients with very low permeation into deeper skin layers [4]. Therefore, many strategies have been proposed to overcome the disadvantages of liposome vesicles. One of the interesting approaches is the use of ethanolic lipid vesicle. ELVs consist of phospholipid, ethanol, and water. The presence of ethanol in these vesicles makes the vesicular membrane highly flexible and malleable, and due to the solvent effect of ethanol, fluidity of stratum corneum lipids increases that leads to enhanced permeability of active ingredient.

One of the widely used plant extracts in cosmetics is essentials oils (EOs). EO is the complex mixtures containing dozens of substances of varying chemical compositions at different concentrations. They are a very important part of the perfume and cosmetic industry, but in the present scenario, their use is not limited to being used as fragrances only. EOs confer several benefits including antifungal [5], antibacterial [6], and antiviral properties [7], and most of these oils also boast powerful antioxidant benefits, which means they have the power to scavenge free radicals to protect the skin from damage [8]. However, their components are labile and volatile, and the sensory perception can be changed as a consequence of oxidation, heating, volatilization, or chemical interactions. These chemical and physical effects, which can alter the quality of products, can be effectively minimized by encapsulating the essentials oils.

In the present work, an attempt has been made to encapsulate Geranium/Calendula essential oil(s) in ethanolic lipid vesicles to prevent their evaporation and to increase their availability and efficacy in cosmetic products to combat skin aging.

2. Material

LipoidS-75 was obtained as a gift sample from Lipoid GmbH (Ludwigshafen, Germany). 2,2-Diphenyl-1-picryl-hydrazyl (DPPH) was obtained as a gift sample from HiMedia Laboratories, Mumbai. Coconut oil, olive oil, naphthylethylene diamine dihydrochloride, sodium nitroprusside, and sulphanilamide were procured from Sigma-Aldrich Chemical Pvt. Limited, Bangalore. Surfactants (tween 60 and span 60), ascorbic acid, geraniol, α-pinene, HPLC grade acetonitrile, water, and methanol were obtained from Central Drug House (P) Ltd., New Delhi. All the chemicals used were of analytical grade. The reagents were prepared using double distilled water.

3. Methods

3.1. Extraction of Essential Oils. In our previous work, we have reported extraction of Geranium essential oil (GEO) from *Pelargonium graveolens* leaves and Calendula essential oil (CEO) from *Calendula officinalis* flowers using a Clevenger apparatus. The extracted EOs were subjected to GC-MS (Gas Chromatography-Mass Spectrometry) analysis to get information about their chemical composition. Citronellol and geraniol were found to be the highly abundant chemical constituents of the GEO. The eminently ample chemical constituents present in CEO were *trans*-β-ocimene, dihydrotagetone, *cis*-tagetone, neo-allo-ocimene, 1,8 cineole, and α-pinene. Our findings showed that GEO and CEO have the potential to reduce or prevent oxidative stress and can be used in skincare regimens to slow down skin aging via its antioxidant properties [9].

3.2. Ethics Declaration. The present investigation was conducted according to the ethical principles and was approved by the Institutional Animal Ethical Committee, School of Pharmaceutical Sciences, IFTM University Moradabad, India (Registration No. 837/ac/04/CPCSEA).

3.3. Formulation of Ethanolic Lipid Vesicles (ELVs)

3.3.1. Preliminary Optimization Studies. Preliminary studies were done to optimize the methodology. Cold method (described later) was used to prepare blank ELVs by varying the concentration of Lipoid S-75 (LS75) in the range of 0.5%*w*/*v*to 5.0%*w*/*v*and ethanol in the range of 10-40% *v*/*v* and analyzed by photomicrographs taken through optical photomicrograph (HICON, Delhi, India) at 100x.

3.3.2. Preparation of Ethanolic Lipid Vesicles. ELVs were prepared by the cold method [5], composed of LS75 (2-3% *w*/*v*), ethanol (20-30% *v*/*v*), and propylene glycol (PG) (10% *v*/*v*). LS75 was dissolved along with the EO in ethanol. This mixture was heated to 30°C ± 1°C, and a fine stream of distilled water was added slowly, with constant mixing at 1000 rpm with a mechanical stirrer in a closed container. The preparation was left to cool at room temperature for 30 min, and then, it was sonicated at 4°C for two cycles of 2 min each with a minute rest between cycles using a sonicator. Various ELV formulations were prepared by varying the concentration of LS75, ethanol, and oil (Table 1).

3.4. Characterization of Essential Oil-Loaded ELVs

3.4.1. Vesicle Size Measurement. The vesicle size and polydispersity index (PDI) of vesicular colloidal suspension were analyzed by a dynamic light scattering technique with Malvern Zetasizer Nano-ZS, Malvern, U.K. with DTS (Nano) software set at an angle of 173°. For vesicle size measurement, the vesicular suspension was diluted with distilled water (1 : 10) and put into the cuvettes of Malvern Zetasizer. Then, the measurements were conducted at 25°C.

3.4.2. Encapsulation Efficiency. Geraniol and α-pinene, one of the major components of GEO and CEO, respectively, were chosen as an index for the determination of encapsulation efficacy (EE). The encapsulation of geraniol and α-pinene was measured by HPLC analysis. The vesicular suspension was transferred into a centrifuge tube and centrifuged for one hour at 30,000 rpm at 4°C using a cooling centrifuge (R-4C, Remi centrifuge, Vasai, India). After centrifugation, the supernatant and sediment were recovered and their volume was measured. Then, the supernatant was lysed using ACN : water (85 : 15) and filtered through a

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Table 1: Composition of ethanolic lipid vesicles.

Formulation code	LipoidS-75 (% *w*/*v*)	GEO (% *w*/*v*)	CEO (% *w*/*v*)	Ethanol (% *v*/*v*)	Propylene glycol (% *v*/*v*)
G1	2	4	—	20	10
G2	3	4	—	20	10
G3	4	4	—	20	10
G4	2	4	—	30	10
G5	3	4	—	30	10
G6	4	4		30	10
C1	2	—	4	20	10
C2	3	—	4	20	10
C3	4	—	4	20	10
C4	2	—	4	30	10
C5	3	—	4	30	10
C6	4	—	4	30	10

nylon filter disc (0.22 μm). The index constituent was assayed both in the sediment and in the supernatant using HPLC to determine the EE [10].

$$\%\text{Encapsulation efficiency} = \frac{\text{Ct} - \text{Cs}}{\text{Cs}} \times 100. \quad (1)$$

Ct is the total amount of oil detected both in supernatant and sediment; Cs is the amount of oil detected in supernatant. The EE was determined in triplicate.

3.4.3. Scanning Electron Microscopy (SEM). Optimized ELVs were visualized using a scanning electron microscope (Hitachi-H7500). A drop of 1% aqueous solution of phosphotungstic acid was added and left in contact with the sample for 5 min. The surplus solution was removed, and the sample was dried at room temperature, and then, the ELVs were viewed under SEM operating at an acceleration voltage of 80 kV.

3.5. Preparation of Cream Formulations

3.5.1. Base Cream. The cream formulation was prepared by the phase inversion technique [11]. The cream composition is given in Table 2. The composition and amount of emulsifying agents were calculated by the HLB method. First of all, the oil constituents like cetyl alcohol, stearic acid, coconut oil, olive oil, and span-60 were mixed in a magnetic stirrer at 100 rpm at 60°C. The aqueous phase contained aloe vera gel and tween 60 as an emulsifying agent. The aqueous phase was added to the oil phase at 60°C with continuous mixing. When the mixture temperature reduced to 50°C, phase inversion took place and the viscosity of the emulsion was increased.

3.5.2. Essential Oil-Loaded Vesicular/Nonvesicular Cream. The constituents and procedure for vesicular cream preparation were the same as those for the base cream, but while preparing vesicular cream, care was taken and the oil-loaded vesicles were added at a temperature below 30°C. In the preparation of nonvesicular cream, EO was added as such without encapsulation into the ELVs.

3.6. Characterization of Cream Formulations

3.6.1. Physical Characterization. All the prepared cream formulations were characterized for color, odor, phase separation, and grittiness by visual observation. A small quantity of cream formulation was pressed between the thumb and index finger. The consistency of the cream was noticed (whether homogeneous or not), if there were any coarse particles that appeared on the fingers. Also, the homogeneity was also detected by rubbing a small quantity of cream on the skin back of the hand. The grittiness was also observed in the same manner.

3.6.2. Spreadability, pH, and Viscosity. The spreadability of cream formulations was calculated by an apparatus suggested by Multimer [12] which is modified accordingly and used for the spreadability study. For the measurement of pH, cream formulations were diluted with distilled water in the ratio of 1 : 10 (cream : water) and mixed properly and their pH was measured by using a digital pH meter [13]. The viscosity of prepared cream formulations was measured by a Brookfield viscometer using T-spindle S-93 at 20 rpm. The temperature was maintained at 25°C ± 1°C. All the procedure was repeated three times, and observations are recorded as mean.

3.6.3. Determination of Percent Essential Oil Content. The percentage content of oil present in the cream was determined by taking 10 mg of the cream and diluting it to 10 ml with the suitable solvent (ACN : water; 85 : 15). The sample was mixed by using a vortex shaker for 40 min and examined by HPLC to determine the percentage of oil present in the cream by measuring the index constituent(s).

3.6.4. Stability Studies of Cream Formulations. The stability of the cream formulation(s) was assessed by storing the formulation at different storage conditions, namely, 8 ± 2°C, room temperature (25-28°C) and at 40 ± 2°C. The physical attributes (color, look, and feel), organoleptic parameters (phase separation, and liquefaction), pH, viscosity, spreadability, and oil content were also observed at various intervals for 30 days [14, 15].

3.7. Determination of Antioxidant Capacity. The antioxidant capacity of GEO- and CEO-based vesicular and nonvesicular cream formulations was determined by the following methods:

DPPH radical scavenging capacity: different dilutions of standard antioxidant (ascorbic acid) and cream formulation were prepared (10-250 μg/ml) in methanol. DPPH solution in methanol (0.1 mM) was added to the equal volume of different dilutions of the sample and standard antioxidant. All the tubes were incubated (30°C) for 30 min in the dark. The absorbance of each solution was measured at 517 nm using a UV-visible spectrophotometer [9].

Nitric oxide scavenging capacity: sodium nitroprusside solution (10 mM) in phosphate buffer (pH 7.4) was added

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Table 2: Composition of various cream formulations, i.e., base cream; vesicular cream (GEO loaded: GC1, GC2, and GC3 and CEO loaded: CC1, CC2, and CC3); nonvesicular cream GEO6 and CEO6 for GEO and CEO, respectively.

Ingredients (% *w*/*w*)	Base cream	GC1	GC2	GC3	GEO6	CC1	CC2	CC3	CEO6
Beeswax	8	8	8	8	8	8	8	8	8
Stearic acid	4	4	4	4	4	4	4	4	4
Cetyl alcohol	3	3	3	3	3	3	3	3	3
Olive oil	12	12	12	12	12	12	12	12	12
Coconut oil	16	16	16	16	16	16	16	16	16
Span60	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4
Tween60	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Aloe vera gel	qs	qs	qs	qs	qs	qs	qs	qs	qs
GEO loaded in vesicles	—	2	4	6	—	—	—	—	—
CEO loaded in vesicles	—	—	—	—	—	2	4	6	—
Free GEO	—	—	—	—	6	—	—	—	—
Free CEO	—	—	—	—	—	—	—	—	6

to the different dilutions (10-250 μg/ml) of sample and standard (ascorbic acid) in methanol. The tubes were incubated (25°C) for 2 hrs. After that, 0.5 ml Griess reagent was added to the incubated tubes and absorbance was measured at 546 nm using a UV-visible spectrophotometer [9].

DPPH and nitric oxide radical scavenging capability was calculated by using following equation:

$$\%\text{Inhibition} = \frac{\text{Ac} - \text{As}}{\text{Ac}} \times 100, \quad (2)$$

where Ac is the absorbance of control and As is absorbance of cream sample/standard.

A linear regression equation was obtained by plotting percent inhibition on the*y*-axis and concentration (μg/ml) on the *x*-axis in a graph, and from this equation, the IC_{50} value was calculated.

Percent inhibition of each sample dilution was plotted by taking on the *y*-axis and concentration (μg/ml) on the *x*-axis in a graph to obtain a linear regression equation, and from this equation, the IC_{50} value (concentration of the sample required to scavenge 50% free radical.) was calculated. The experiment was done in triplicate.

3.8. Determination of Sun Protection Factor (SPF) of Cream Formulations. For practical, economical, and ethical reasons, the *in vitro* SPF measurement techniques represent an acceptable and speedy tool for shortening *in vivo* risks and experiments related to UV exposure of human subjects. *In vitro* SPF of cream formulations was determined as per the COLIPA standards [16] which include the measurement of the percent transmittance of a sunscreen product across the UV spectrum weighted by the erythemal weighting factors at different wavelengths [17].

$$\text{SPF}_{\text{spectrophotometric}} = \text{CF} \times \sum_{290}^{320} \text{EE}(\lambda) \times I(\lambda) \times \text{Abs}(\lambda), \quad (3)$$

where CF is correction factor (10), EE(λ) is erythmogenic effect of radiation with wavelength λ, and Abs (λ) is spectrophotometric absorbance values at wavelength λ. The values of EE (λ) $\times I$ are constants.

3.9. In Vitro Enzyme Inhibition Assay. After getting the results from *in vitro* antioxidant assays and SPF determination, optimized cream formulations (GC3 and CC3) were selected for the *in vitro* enzyme inhibition assay.

3.9.1. In Vitro Collagenase Inhibition Assay. For this assay, 1, 10, 50, 100, 500, and 1000 μg/ml concentration of selected cream samples in ethanol was prepared. 5 μl of each concentration of test sample was taken in a reaction mixture along with enzyme in total volume of 80 μl, and the reaction mixture was incubated for 15 minutes. After incubation, 20 μl of the substrate (FALGPA) was added to each reaction mixture and readings were recorded at 345 nm/660 nm for 10 min at 1 min interval. Epigallocatechin gallate (EGCG) was taken as positive control.

3.9.2. In Vitro Elastase Inhibition Assay. In this assay, 1, 10, 50, 100, 500, and 1000 μg/ml concentration of selected cream samples in ethanol was prepared. 5 μl of each concentration was taken in reaction mixture along with elastase enzyme in total volume of 90 μl, and the reaction mixture was incubated for 15 minutes. After incubation, 10 μl of the substrate (N-succinyl-Ala-Ala-Ala-p-nitroanilide) was added to each reaction mixture and the readings were recorded at 405 nm/660 nm for 10 min at 1 min interval. Epigallocatechin gallate (EGCG) was taken as positive control.

In both the enzyme inhibition assays, the percent inhibition was calculated by using the following equation:

$$\%\text{Inhibition} = \frac{\text{AbC} - \text{AbS}}{\text{AbC}} \times 100, \quad (4)$$

where AbC is absorbance of control and AbS is absorbance of sample/standard.

3.10. Skin Irritation Study. Albino rats of either sex, weighing 150-180 g, were used for skin irritation study ($n = 3$ in each group). The animals were divided into two groups,

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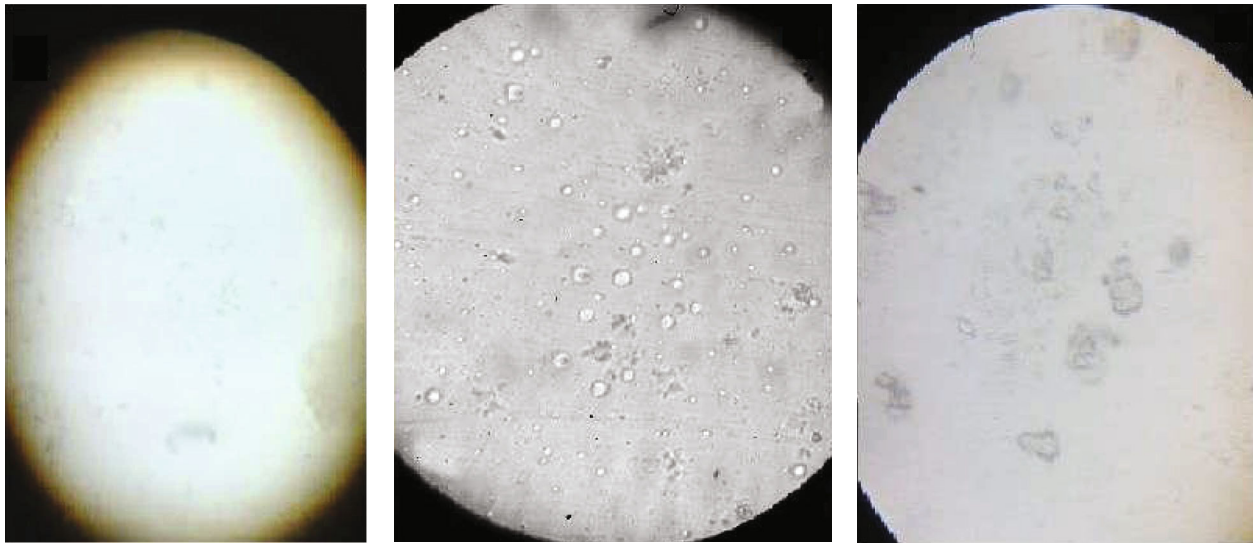

(a) (b) (c)

FIGURE 1: Optical microscopic image of prepared vesicles at different concentrations of LS75: (a) below 2% *w*/*v* (vesicles could not form); (b) 2-4% *w*/v (spherical vesicles with well-defined boundaries); (c) above 4% *w*/*v* (larger vesicles with irregular shape).

namely, the controlled and test groups. Before three days of starting the study, hair was shaved from the back of rats and a 5 cm^2 area was marked. The cream formulations were applied to the marked site, and the site was observed for any reaction or sensitivity and slight/moderate or severe erythema till 3 days after application. To score the skin reactions for erythema, scar, and edema, the Draize skin irritation scoring system was selected [18]. The reactions, defined as erythema and edema, were evaluated according to the scoring system for skin reactions. The score of primary irritation (SPI) was calculated for each rat. Scores for erythema and edema at 24, 48, and 72, hours were summed and divided by the number of the observations for the treated sites. The SPI for the control sites were calculated in the same fashion as the test.

3.11. Confocal Laser Scanning Microscopy (CLSM) Study. Skin permeation depth and mechanism of rhodamine red-loaded vesicles were examined by CLSM. Rhodamine-loaded vesicular cream was formulated by adding the dye to the mixture of LS75 in ethanol and PG, and the prepared dye-loaded vesicles were incorporated into the cream base. Dye-loaded vesicular and the nonvesicular cream formulation was applied to the dorsal rat skin for 8 h. The rats were sacrificed, and the skin was excised and washed. The skin sections were prepared and examined with CLSM (Fluoview FV 1000, Olympus, Japan) [19].

4. Results and Discussion

4.1. Formulation of ELVs. Phospholipid and ethanol are the basic materials composing ELVs and play an important role in vesicle characteristics such as size, entrapment efficacy, and stability. The phospholipid is responsible for the formulation of a lipid bilayer that affects the stability of the vesicle and also enhances the rigidity and prevents leakage of the enclosed material. The optimum concentration of ethanol enhances the membrane elasticity and fluidity of vesicles that may contribute to high skin permeability.

Preliminary screening studies were carried out to identify the effect of variables that influence the physicochemical properties of vesicles and to optimize the methodology. Placebo (blank) ELVs were prepared by using varied concentration of LS75 (0.5%-4.0% *w*/*v*) and ethanol (10-40% *v*/*v*). The results showed that below 2% *w*/*v* concentration of LS75, the vesicles could not form (Figure 1(a)). It was observed that between 2-4% *w*/*v* of LS75, the vesicles were uniformly distributed with spherical shape and well-defined boundaries (Figure 1(b)) and above 4% *w*/*v* larger vesicles were formed with irregular shape (Figure 1(c)). ELVs were formulated by using LS75 in the concentration range of 2-4% *w*/v and ethanol in the range of 30-40% *v*/*v*.

4.2. Characterization of Essential Oil-Loaded ELVs

4.2.1. Vesicle Size Measurement. Vesicle size is one of the important parameters that affect the permeability across the skin. Developed EO-loaded ELVs were varied in the size range of 192.0 nm-543.1 nm (Table 3). The vesicle size distribution diagram of optimized formulations (G6 and C6) is shown in Figure 2. The results showed that vesicle size was directly proportional to the concentration of LS75 and indirectly proportional to the concentration of ethanol [20], i.e., as the concentration of LS75 was increased, vesicle size was also increased and upon increasing the concentration of ethanol, the size of vesicles got reduced. It has been reported in the previous studies that a high concentration of ethanol leads to the interpenetration of the ethanol hydrocarbon chain, which results in slimming down of vesicle membrane thickness and hence causes a reduction in vesicle size. Some researchers have suggested that this may be due to the fact that high concentration of ethanol modifies the vesicular

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Table 3: Results of vesicle size, polydispersity index, and encapsulation efficiency of ethanolic lipid vesicles.

S. No.	Formulation code	Vesicle size (nm)	Polydispersity index (PDI)	Encapsulation efficiency (%)
1	G1	411.3	0.292	58.92 ± 0.33
2	G2	458.9	0.089	62.62 ± 0.64
3	G3	543.1	0.274	78.95 ± 0.69
4	G4	218.3	0.131	68.24 ± 0.87
5	G5	245.9	0.288	80.95 ± 0.49
6	G6	199.6	0.063	89.00 ± 0.85
7	C1	339.5	0.208	60.24 ± 0.78
8	C2	399.1	0.292	69.52 ± 1.64
9	C3	424.7	0.301	78.39 ± 0.61
10	C4	185.0	0.172	72.81 ± 0.46
11	C5	220.1	0.045	84.60 ± 0.82
12	C6	192.0	0.107	90.95 ± 0.29

surface characteristics and alters the net charge, which could lead to a decrease in mean vesicle size [21].

4.2.2. Polydispersity Index (PDI). PDI number is a description of the dispersion of size populations within a given sample. The stability of vesicular formulation depends upon the homogenous populations of vesicles of a certain size. PDI number ranges from 0.0 to 1.0. The best PDI value is 0.0 which indicates homogenous dispersion with respect to the vesicle size, and the PDI value 1.0 indicates an extremely polydisperse sample with multiple vesicular size populations [22]. In the case of lipid-based vesicular carriers, a PDI value of 0.3 and below is considered to be agreeable and shows a homogenous dispersion of lipid vesicles [23, 24]. The results showed that all the vesicular formulations have a PDI value less than 1.0 and ranged from 0.045 to 0.301, which indicates that vesicles are homogenously distributed (Table 3).

4.2.3. Encapsulation Efficiency. EE of vesicular formulations is the part of total oil entrapped in the prepared vesicles, which determines the oil holding capacity and ultimately the delivery potential to the particular site. The EE was found to be in the range from 58.92 ± 0.33% to 90.95 ± 0.29% (Table 3). Results showed that both the amount of LS75 and the concentration of ethanol influence the encapsulation of oil in vesicles positively. It was noticed that with the increase in the concentration of LS75 from 2% to 4% and ethanol from 20% to 30% ,the entrapment of oil inside the vesicles also increased. Based on the physicochemical characterization, the optimized vesicular formulations G6 (GEO encapsulated) and C6 (CEO encapsulated) were selected for visualization.

4.2.4. Scanning Electron Microscopy (SEM). SEM results of optimized ethanolic lipid vesicles loaded with GEO and CEO, i.e., G6 and C6, respectively, disclosed the dominance of spherical vesicular carriers as shown in Figure 3.

4.3. Selection of Optimized ELVs. Based on the results obtained from the characterization of ELVs, G6 (GEO encapsulated) and C6 (CEO encapsulated) were selected for incorporation into the cream base.

4.4. Characterization of Cream Formulations

4.4.1. Physical Characterization. All the cream formulations were white in color with a mild characteristic odor of the EO used. The prepared cream formulations were homogeneous with a complete absence of lumps and grittiness.

4.4.2. Spreadability, Viscosity, and pH. A cream should not generate friction while applied on the skin and should spread easily. Spreading quality of cream helps in the uniform application to the skin. The spreadability result of prepared creams was found in the range of 17.68 ± 0.34 gm·cm/sec to 25.50 ± 0.45 gm·cm/sec. The results express the ability of the creams to spread on the application of a small amount of shear. The spreadability characteristics are also influenced by viscosity. The viscosity of the cream formulations ranged between 2713.5 ± 1.02 and 6011.2 ± 1.20 cp which indicate substantial consistency. Furthermore, the pH values of all developed formulations were in the range 6.8 ± 0.052 gm·cm/sec to 7.1 ± 0.050 gm·cm/sec (Table 4). The pH values lie in the normal pH range of the skin and would not produce irritation upon application to the skin.

4.4.3. Determination of Percent Essential Oil Content. The EO content determination results indicated that the EO was uniformly distributed throughout the vesicular cream formulation. It was interesting to observe that in the case of free EO-loaded creams, the EO content results were significantly reduced; this might be due to the loss of free EO during the cream formulation process (Table 4).

4.5. Stability Studies of Cream Formulations. The motive behind stability testing of a cosmetic product is to confirm that the tested product meets the intended chemical and physical quality standards, functionality, and aesthetics when stored under suitable storage conditions. The freshly prepared creams were white in color, but a slight change in color was observed for GC1 formulation after 30 days and for CC1 after 21 days when stored at 40°C; this may be due to the separation of the oil phase at high temperature. No sign of liquefaction was observed in the tested creams at different storage conditions for 30 days of observation. There was no phase separation in any tested creams after centrifugation and freeze and thaw test. It was observed that the freezing lowered the viscosity of tested creams [25]. The absence of any sign of liquefaction and phase separation provided strong evidence for the stability of the creams under investigation.

There was no significant change in the pH value of tested creams at various storage conditions. The oil content in creams decreased at higher temperature suggesting storage at room temperature or cool place. None of the stability parameters changed significantly at room temperature.

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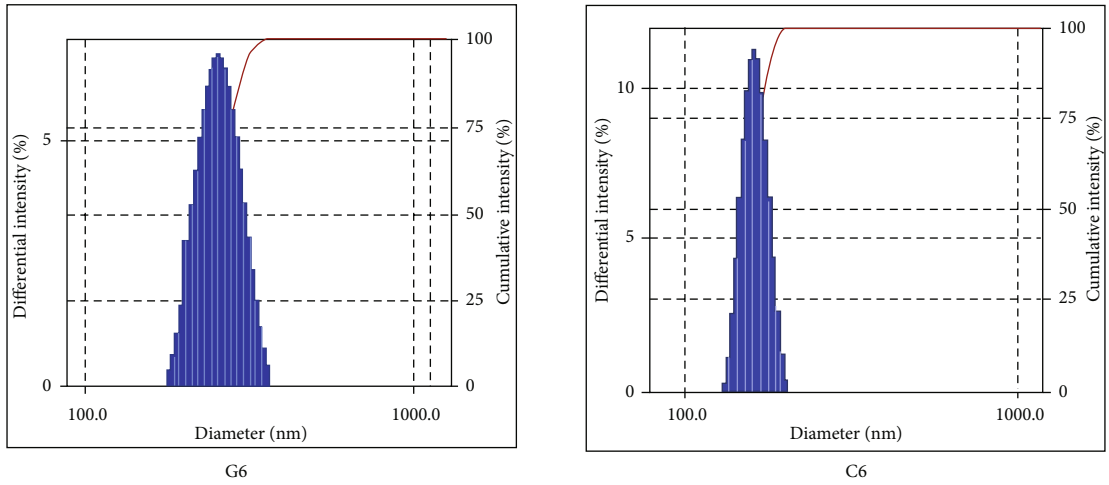

Figure 2: Vesicle size distribution diagram of optimized ethanolic lipid vesicles (G6 and C6).

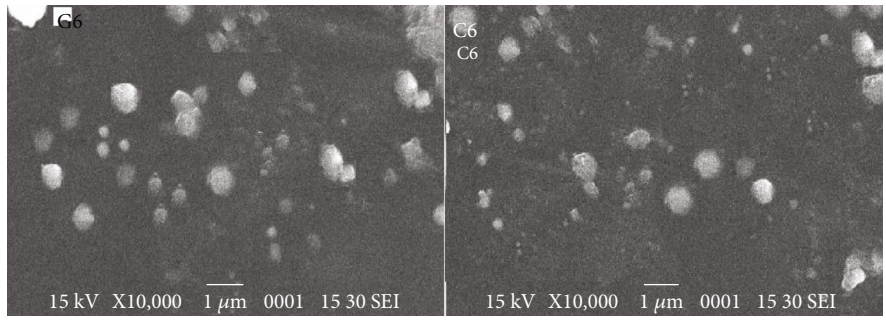

Figure 3: SEM image of optimized ethanolic lipid vesicles: G6 (GEO encapsulated) and C6 (CEO encapsulated).

Table 4: Characterization of GEO-/CEO-based vesicular and nonvesicular cream formulations.

Formulation code	Spreadability (gm·cm/sec)	pH	Viscosity (cp)	EO content (%)
Base cream	17.68 ± 0.34	6.8 ± 0.052	2713.5 ± 1.02	—
GC1	20.68 ± 0.56	7.0 ± 0.091	5413.5 ± 1.60	90.46 ± 1.98
GC2	22.82 ± 0.82	6.9 ± 0.056	5402.0 ± 1.58	93.78 ± 1.05
GC3	25.50 ± 0.45	6.9 ± 0.048	6011.2 ± 1.20	98.23 ± 1.60
CC1	18.06 ± 0.92	6.8 ± 0.060	5424.5 ± 2.60	95.62 ± 1.90
CC2	20.42 ± 0.42	7.1 ± 0.050	4302.5 ± 2.01	97.48 ± 2.01
CC3	22.49 ± 0.60	7.0 ± 0.078	4413.5 ± 1.98	98.66 ± 1.50
GEO6	20.60 ± 0.74	7.0 ± 0.028	2878.5 ± 1.02	74.78 ± 2.20
CEO6	18.68 ± 0.90	6.9 ± 0.040	4028.6 ± 1.00	71.89 ± 1.82

4.6. Determination of Antioxidant Capacity. Antioxidants are capable to guard against skin damage and slow down the skin aging process. The antioxidant capacities of extracted GEO and CEO have been previously reported by us [9], and their assessment of the antioxidant capacity after formulation as ELV-based cream was carried out.

4.6.1. Nitric Oxide Scavenging Capacity. Sodium nitroprusside decomposes in an aqueous physiological solution (at pH 7.4) results in the generation of nitric oxide. Nitric oxide is a free radical that reacts with oxygen under aerobic conditions and generates nitrite ions. The principle of this scavenging technique relies on the measurement of the capacity of the antioxidant to trap nitric oxide, leading to a decreased production of nitrite ions. The results of nitric oxide scavenging capacity are shown in Figure 4. The nitric oxide scavenging capacity of the standard (ascorbic acid) was 89.19 ± 0.05% at 250 μg/ml. The nitric oxide scavenging capacity of extracted EOs was previously reported by us as 85.15 ± 0.09% and 72.48 ± 0.12% for GEO and CEO,

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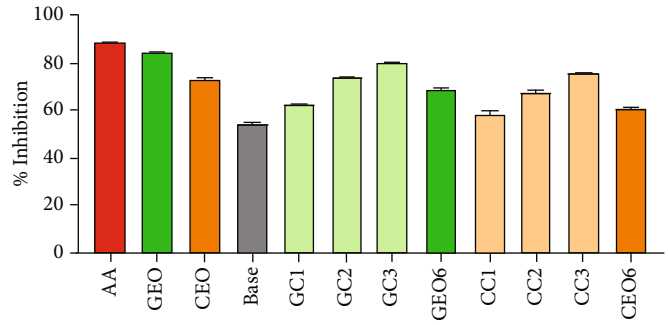

Figure 4: Comparison of nitric oxide scavenging capacity of standard (AA); essential oils (GEO and CEO); base cream; GEO-loaded vesicular creams (GC1, GC2, and GC3); CEO-loaded vesicular creams (CC1, CC2, and CC3); and nonvesicular cream GEO6 and CEO6 for GEO and CEO, respectively.

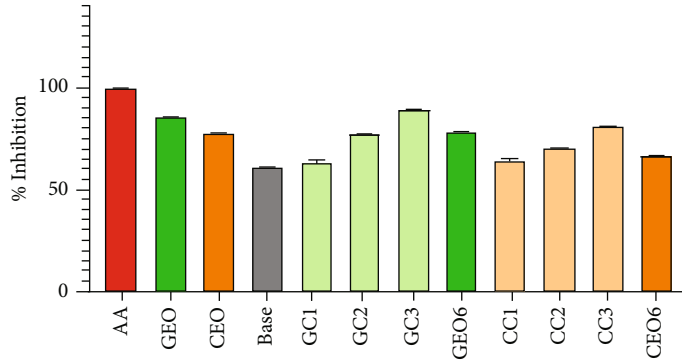

Figure 5: Comparison of DPPH radical scavenging capacity of standard (AA); essential oils (GEO and CEO); base cream; GEO-loaded vesicular creams (GC1, GC2, and GC3); CEO-loaded vesicular creams (CC1, CC2, and CC3); and nonvesicular cream GEO6 and CEO6 for GEO and CEO, respectively.

respectively [9]. In the case of GEO-/CEO-loaded vesicular and nonvesicular cream formulations (Figure 3), the maximum inhibition was shown by GC3 ($80.96 \pm 0.20\%$) and CC3 ($75.21 \pm 0.31\%$) formulation for GEO and CEO, respectively.

4.6.2. DPPH Scavenging Capacity. In this method, the degree of DPPH radical discoloration is often used as an index of the antioxidant capacity of the tested samples. In our previous work [9], we observed that GEO has a higher power to diminish the dark violet color of DPPH radical to yellow diphenylpicrylhydrazine radical in comparison to CEO and that GEO was found to be rich in monoterpenoid and citronellol and geraniol were the major component of the oil and they also have been previously identified as a potential antioxidant [26, 27]. The DPPH radical scavenging capacity of extracted EOs was previously reported by us as $85.51 \pm 0.020\%$ (for GEO) and $78.06 \pm 0.04\%$ (for CEO) at $250\,\mu g/ml$ [9].

The highest DPPH radical scavenging capacity ($99.08 \pm 0.08\%$) was obtained by standard ascorbic acid in the concentration of $250\,\mu g/ml$. At the same concentration, the maximum percent inhibition was shown by GC3 ($89.82 \pm 0.11\%$) and CC3 ($80.89 \pm 1.03\%$) formulation, respectively (Figure 5). The DPPH radical scavenging capacities of EO-loaded vesicular cream formulations were found to be remarkable in comparison to standard antioxidant and EO alone.

The results of both the antioxidant assay showed that GEO- or CEO-loaded vesicular cream formulations have notable antioxidant capacity when compared to EO alone. The results were eye-catching when the antioxidant capacity of vesicular cream formulations was compared with the cream formulation containing the same concentration of unentrapped or free EO. It was interesting to observe that with both the EOs, the scavenging capacity was reduced for nonvesicular cream formulation in comparison to the same concentration of vesicular cream. This may be due to the instability or loss of EO during the formulation of nonvesicular cream formulation.

4.7. Determination of In Vitro Sun Protection Factor. In vitro SPF determination is a useful test for screening ingredients during the development stage of a cosmetic product. The higher the SPF, the more the protection offered by sunscreen against UV light. An EO should absorb major UV radiations (290-400 nm) to be adequately used in cosmetic formulations to prevent photoaging, sunburn, skin wrinkles, and other skin damages. In our previous work, the SPF value of GEO and CEO was found to be 6.45 and 8.36, respectively [9]. EO-based vesicular cream formulations showed remarkably high SPF in comparison to EO alone. The SPF value of

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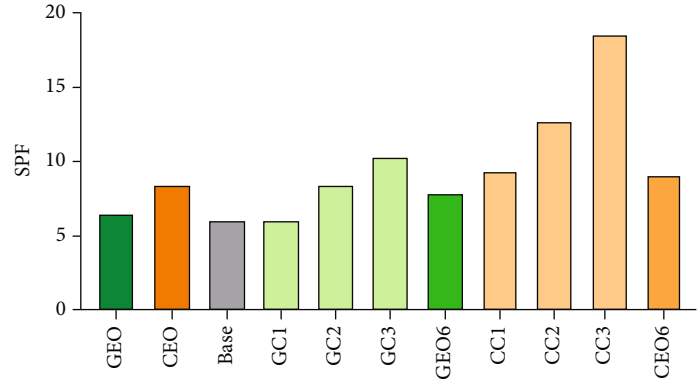

Figure 6: Comparison of *in vitro* SPF values of essential oils (GEO and CEO), base cream, GEO-loaded vesicular creams (GC1, GC2, and GC3), CEO-loaded vesicular creams (CC1, CC2, and CC3), and free oil-loaded nonvesicular cream GEO6 and CEO6 for GEO and CEO, respectively.

GEO-loaded vesicular cream was found to be 6.02, 8.35, and 10.26 for GC1, GC2, and GC3, respectively (Figure 6). The SPF of CEO-loaded vesicular cream was found to be 9.28, 12.68, and 18.54 for CC1, CC2, and CC3, respectively. The SPF of free EO-loaded nonvesicular cream formulation was 7.82 (for GEO) and 9.02 (for CEO) which is very low in comparison to the vesicular cream at the same concentration of EO. The overall results showed that CEO-based cream formulation had higher SPF in comparison to GEO-based cream formulation.

4.8. In Vitro Enzyme Inhibition Assay. One of the main reasons behind various signs of skin aging is the damage and loss of two key proteins: collagen and elastin [28]. These proteins are essential for maintaining youthful skin, which are found in the deeper layers of the skin. Collagen plays a major role in skin strengthening, and elastin allows the body tissues to return to their original shape either by contracting or stretching. These proteins are essential for skin and work together to create skin firmness and help to hold the skin shape and strength [29, 30]. The main cause of degradation of these proteins is matrix metalloproteinases (MMPs). MMP enzymes such as collagenase and elastase are responsible for the breakdown of collagen and elastin protein, respectively. Degradation of the two essential skin proteins by these enzymes accelerates skin wrinkling and sagging skin appearance and leads to skin aging. Thus, it is important to determine the enzyme inhibiting activity of the developed formulations in order to assess the antiaging potential. This is the first-time research to investigate the antielastase, anticollagenase potential of GEO-/CEO-based formulation. The optimized cream formulations (GC3 and CC3) from each EO were used for further investigation of enzyme inhibition assay.

4.8.1. In Vitro Collagenase Inhibition Assay. The assay is based on an enzyme-substrate interaction, i.e., between collagenase enzyme and the synthetic collagen substrate N-[3-(2-furyl) acryloyl]-Leu-Gly-Pro-Ala (FALGPA). Proteolytic degradation of this collagen substrate due to the collagenase enzyme results in a decrease in absorbance. Collagenase inhibitors prevent the degradation of FALGPA [31]. The EOs incorporated in the creams have potential for collagenase inhibition that was assessed by the assay. From the results of the collagenase inhibition assay, it was observed that both the formulations showed anticollagenase activity in a concentration-dependent manner (Figure 7). It was observed that the anticollagenase activity increases as the concentration increases from 1 to 100 μg/ml. In the case of GC3, formulation maximum inhibition (28.4%) was observed at 1000 μg/ml, whereas at the same concentration, CC3 showed the maximum inhibition of 22.9%.

4.8.2. In Vitro Elastase Inhibition Assay. The elastase inhibition assay is based on the fact that the enzyme (elastase) causes the breakdown of the elastin substrate (N-succinyl-Ala-Ala-Ala-p-nitroanilide) and yields fluorescent fragments that are measured using a fluorescence microplate reader. This enzymatic hydrolysis is interrupted by the elastase inhibitors [32]. The elastase inhibition activity of the developed creams was assessed to determine their antiaging potential. The antielastase activities of both the optimized cream formulations (GC3 and CC3) are shown in Figure 8. The antielastase activity was found to be in a concentration-dependent manner. In the case of GEO-loaded vesicular cream formulation (GC3), it was surprising to see that the antielastase inhibition was higher (144.0%) than ECGC (122.4%) at the concentration of 1000 μg/ml. CEO-loaded vesicular cream formulation (CC3) also showed significant elastase inhibition activity. The highest antielastase inhibition was observed at 108.2% at the same concentration i.e., 1000 μg/ml.

The findings have verified that the GEO-/CEO-loaded vesicular creams may contribute to the fight against skin aging by preventing collagen and elastin degradation underneath the skin and can help to restore skin strength and elasticity and thereby slow down the skin wrinkling process.

4.9. Skin Irritation Study. In this study, rats were divided into 5 groups ($n = 3$ in each group). In group 1, base cream was applied, in groups 2 and 3 optimized vesicular cream of each EO (GC3 and CC3), and in groups 4 and 5

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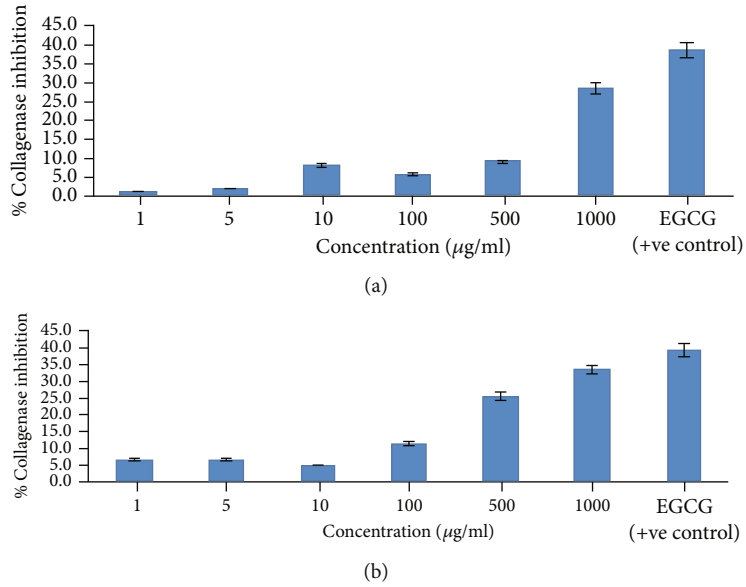

Figure 7: *In vitro* collagenase inhibition assay: (a) % collagenase inhibition shown by GEO-loaded optimized cream formulation GC3; (b) % collagenase inhibition shown by CEO-loaded optimized cream formulation CC3.

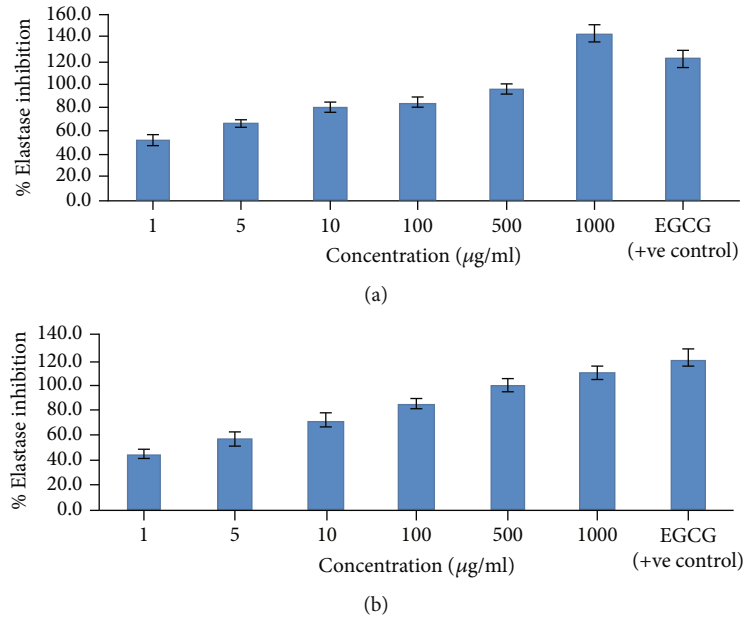

Figure 8: *In vitro* elastase inhibition assay: (a) % elastase inhibition shown by GEO-loaded optimized cream formulation GC3; (b) % elastase inhibition shown by CEO-loaded optimized cream formulation CC3.

nonvesicular cream formulation of each EO (GEO6 and CEO6). The results obtained from the primary skin irritation studies (Table 5) interpreted according to Draize test [17] which says that test samples that produce PII scores of 2 or less are considered negative, i.e., no skin irritation. Since, the score between 0 and 2 suggests no to mild irritation, thus, low PII of vesicular cream formulation (0.27 for GC3 and 0.16 for CC3 cream formulations) in comparison to base cream (0.16) observed in the study depicted nonirritancy of the cream formulation and could be considered safe for use, while the primary skin irritation studies of free EO-loaded nonvesicular cream showed high PII values (0.55 for GEO6 and 0.49 for CEO6 cream formulation) which indicates slight skin irritation in comparison to vesicle-based cream formulations of the same EO.

4.10. Confocal Laser Scanning Microscopy (CLSM) Study. Cream formulations loaded with and without lipid vesicles were prepared, and penetration across the skin was measured by CLSM study. Skin permeation of rhodamine (marker) from rhodamine-loaded nonvesicular cream and rhodamine-loaded vesicular cream formulation was visualized through a confocal laser scanning microscope. It was observed that permeation from rhodamine-loaded nonvesicular cream

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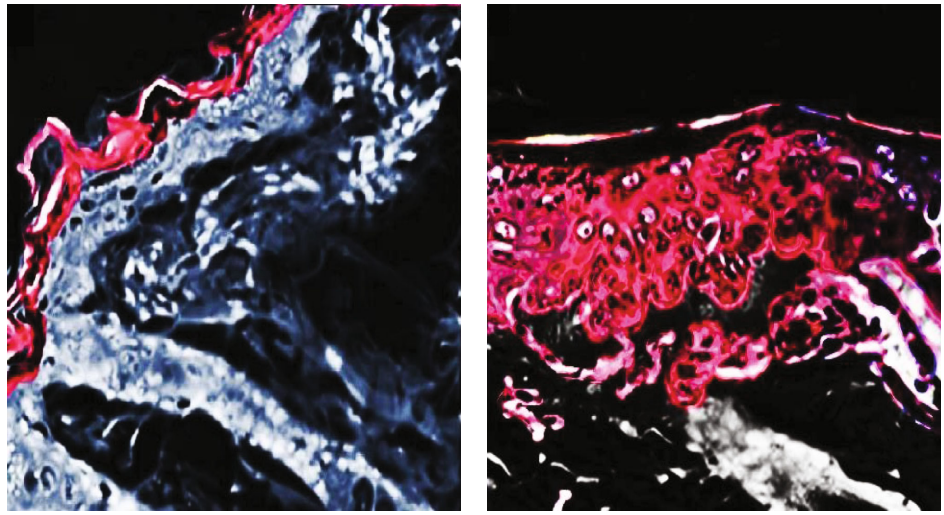
Table 5: Skin irritation study scores for primary irritation and primary irritation index measured at 24, 48, and 72 hrs after applying the cream formulations on the rat skin.

(a)

Skin reaction	Time (hrs)	Group 1 (cream base)			Group 2 (formulation GC3)			Group 3 (formulation CC3)		
		Rat-1	Rat-2	Rat-3	Rat-1	Rat-2	Rat-3	Rat-1	Rat-2	Rat-3
Erythema	24	1	1	1	1	1	1	1	0	0
	48	0	0	0	0	0	0	0	0	0
	72	0	0	0	0	0	0	0	0	0
Edema	24	0	0	0	1	0	1	1	1	0
	48	0	0	0	0	0	0	0	0	0
	72	0	0	0	0	0	0	0	0	0
Score of primary irritation		0.16	0.16	0.16	0.33	0.16	0.33	0.33	0.16	0.0
Primary irritation index			0.16			0.27			0.16	

(b)

Skin reaction	Time (hrs)	Group 4 (GEO6)			Group 5 (CEO6)		
		Rat-1	Rat-2	Rat-3	Rat-1	Rat-2	Rat-3
Erythema	24	1	1	1	1	1	1
	48	1	0	1	1	1	1
	72	0	0	0	0	0	0
Edema	24	1	1	1	1	1	0
	48	1	0	1	0	1	0
	72	0	0	0	0	0	0
Score of primary irritation		0.66	0.33	0.66	0.50	0.66	0.33
Primary irritation index			0.55			0.49	



(a) (b)

Figure 9: CLSM of (a) Rhodamine-loaded nonvesicular cream confined to the upper layer of the skin epidermis; (b) enhanced skin permeation observed by rhodamine-loaded vesicular cream.

(Figure 9(a)) was confined only to the upper layer of the skin epidermis, while in the case of rhodamine-loaded vesicular cream (Figure 9(b)), enhanced permeation of rhodamine was observed deep into the skin layers. This shows that prepared ELVs have the ability to carry antiaging EO deep into the skin where the root cause of skin aging exists.

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5. Conclusion

Finding solutions against the signs of skin aging has been a natural human desire for centuries. Because of this, the market is flooded with beauty care products claiming magical results within a short period of application. It is to be noted that natural aging is genetically determined, but extrinsic aging can be slowed down with the use of scientifically designed and evaluated cosmetic formulations. The need of the hour is to put serious efforts into the development of such products, which actually translate the stated claims in the case of extrinsic aging. From the research findings, the antioxidant potential, ability to inhibit collagenase and elastase enzyme, and photoprotective effects of GEO/CEO vesicular cream were confirmed. Results clearly showed that ELVs were able to preserve the efficiency of essential oils and have the potential to deliver the actives deeper into the skin. Essential oil-encapsulated vesicular creams were able to provide antioxidant defence mechanism with high SPF and are able to protect the skin in comparison to free essential oil-loaded nonvesicular creams. The cumulative effect of ELVs and cream composition and essential oil will collectively produce a protective effect to combat skin aging.

Data Availability

Data are available in Supplementary files. Supplementary data supporting the findings of this study includes the image of optimized cream formulations, detailed results of antioxidant capacity, and SPF values of prepared cream formulations.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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Supplementary Materials

Supplementary data supporting the findings of this study includes the image of optimized cream formulations, detailed results of antioxidant capacity, and SPF values of prepared cream formulations. *(Supplementary Materials)*

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