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# Development and Characterization of Pullulan-Based Orodispersible Films of Iron

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## Abstract

Iron deficiency is the principal cause of nutritional anemia and it constitutes a major health problem, especially during pregnancy. Despite the availability of various non-invasive traditional oral dosage forms such as tablets, capsules, and liquid preparations of iron, they are hard to consume for special populations such as pregnant women, pediatric, and geriatric patients with dysphagia and vomiting tendency. The objective of the present study was to develop and characterize pullulan-based iron-loaded orodispersible films (i-ODFs). Microparticles of iron were formulated by a microencapsulation technique, to mask the bitter taste of iron, and ODFs were fabricated by a modified solvent casting method. Morphological characteristics of the microparticles were identified by optical microscopy and the percentage of iron loading was evaluated by inductively coupled plasma optical emission spectroscopy (ICP-OES). The fabricated i-ODFs were evaluated for their morphology by scanning electron microscopy. Other parameters including thickness, folding endurance, tensile strength, weight variation, disintegration time, percentage moisture loss, surface pH, and in vivo animal safety were evaluated. Lastly, stability studies were carried out at a temperature of 25 °C/60% RH. The results of the study confirmed that pullulan-based i-ODFs had good physicochemical properties, excellent disintegration time, and optimal stability at specified storage conditions. Most importantly, the i-ODFs were free from irritation when administered to the tongue as confirmed by the hamster cheek pouch model and surface pH determination. Collectively, the present study suggests that the film-forming agent, pullulan, could be successfully employed on a lab scale to formulate orodispersible films of iron. In addition, i-ODFs can be processed easily on a large scale for commercial use.


**Keywords: anemia (/search?q=anemia)**; **iron (/search?q=iron)**; **orodispersible film (/search?q=orodispersible+film)**; **plasticizer (/search?q=plasticizer)**; **pullulan (/search?q=pullulan)**

## 1. Introduction

Iron (Fe) is a key micronutrient essential for various biochemical functions in the human body. Its deficiency impacts oxygen transportation and enzymatic reactions involved in various metabolic pathways [**1**]. Progressive augmentation in iron deficiency would lead to a medical condition called ‘Anemia’ or more specifically ‘Iron Deficiency Anemia (IDA)’ [**2**]. Subjects such as pregnant women and children are highly vulnerable groups to IDA. This medical condition is determined based on the

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percentage of hemoglobin (Hb) present in red blood cells. As per the World Health Organization, adult males are said to be anemic if the Hb value is <13.0 g/dL. Similarly, females and pregnant women are called anemic if the Hb values are <12.0 g/dL and <11.0 g/dL, respectively [**3**]. Various strategies exist to counter IDA that include but are not limited to iron supplementation or iron food fortification using various salts of iron [**4**]. Clinically, various non-invasive traditional oral dosage forms (tablets, capsules, and liquid preparations) of iron are commonly used as the first line of therapy [**5**]. Nevertheless, they are hard to consume for special populations such as pregnant women, pediatric, and geriatric patients with dysphagia, vomiting tendency, bipolar disorder, oral cancer, and Parkinson's disease [**6**,**7**,**8**,**9**]. Moreover, these dosage forms also cause dose-dependent side effects such as gastric upset, diarrhea, nausea, metallic taste [**10**], and changes in the gut microbiome [**11**,**12**,**13**]. At the same time, the parenteral administration of iron is associated with various disadvantages. For instance, intramuscular administration leads to local reactions such as pain, skin staining (brown), atrophy, necrosis, and immediate reaction like anaphylactic shock. Similarly, intravenous administration of iron may lead to phlebitis and various systemic reactions such as fever, dizziness, myalgia, arthralgia, and vomiting [**14**]. Nonetheless, in very severe IDA (Hb < 8.0 g/dL), parenteral iron therapy is preferred due to its superior rapidity and efficacy [**15**].

The above-mentioned limitations in general and the difficulties of the special population, in particular, highlight the need for a novel drug delivery system. Accordingly, the pharmaceutical and clinical research industries have witnessed a transition in oral drug delivery from traditional dosage forms (tablets or injections) to a new non-invasive concept of rapidly dispersing orodispersible films (ODFs) [**16**,**17**]. ODFs are ultra-thin, portable, and postage-stamp-sized dosage forms that 'rapidly disperse when administered to the tongue and swallowed naturally along with the saliva to get absorbed into the systemic circulation via the gastrointestinal tract' [**17**]. Most importantly, compared to traditional dosage forms, ODFs do not need water for administration and are easy to administer to patients across all age groups [**18**]. Thus, they are especially well-positioned to meet the requirements of the special population (pediatrics geriatrics, and pregnant women) suffering from dysphagia, nausea/vomiting, and other conditions or diseases stated above [**6**,**7**,**9**].

Various film-forming polymers are employed in the fabrication of ODFs, such as maltodextrin [**19**], polyvinyl alcohol [**20**], hydroxypropyl methylcellulose [**21**], and pullulan [**22**]. These polymers offer tremendous support in maintaining the film's mechanical properties, disintegration and dissolution, and good quality with an acceptable mouthfeel. Of particular interest, pullulan is a natural, biocompatible, biodegradable, non-ionic, water-soluble material obtained from the black yeast *Aureobasidium pullulan* [**23**,**24**]. Pullulan has been used in film formulations of various drugs and has been found to be a safe and non-toxic material [**25**,**26**]. Accordingly, in this study pullulan was employed as a polymer in the formulation of i-ODFs.

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Generally, the most commonly used source of iron supplements for therapeutic and prophylactic use is ferrous sulfate, which is freely soluble in water [**27**,**28**]. However, its use is associated with common side effects such as the darkening of teeth, nausea, abdominal pain, and black/ dark stools [**29**,**30**,**31**,**32**]. To overcome these issues, compounds such as ferrous succinate, ferrous fumarate, and ferric saccharate have evolved, which are poorly soluble in water but soluble in dilute hydrochloric acid, have less organoleptic issues compared to ferrous sulfate, and readily enter the common iron pool during digestion [**33**]. Nevertheless, these salts are not bioavailable and need effective taste masking, since the acceptability of any ODF depends predominantly on its taste. Hence, the taste of the ODF is a crucial factor to gain end-user acceptance and thereby compliance. Therefore, effective strategies to taste-mask the active substance need to be developed to formulate an ideal ODF [**34**].

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Accordingly, in light of the above rationale and background of iron and pullulan, the objective of the present study was to develop a palatable, rapidly dispersing, non-irritant, and readily bioavailable pullulan-based iron-loaded ODF (i-ODF) for prophylactic use in subjects across all age groups and especially for people with special needs.

## 2. Materials and Methods

### *2.1. Materials*

Ferric saccharate was obtained from Biodeal Pharmaceuticals (New Delhi, India). The film-forming polymer, pullulan, was purchased from Kumar Organics (Bangalore, India). Sodium alginate, calcium acetate, and all other pharmaceutically acceptable excipients employed in the formulation of the ODFs were purchased from S.D. Fine Chemicals Ltd. (Mumbai, India). All other chemicals and solvents used were of analytical grade.

### *2.2. Preparation of Microencapsulated Iron Particles*

**Table 1** provides details of the composition to fabricate microencapsulated or microparticles (MPs) of iron (Fe). The fabrication steps include dissolving sodium alginate and ferric saccharate in 100 mL of distilled water to obtain a viscous mixture. The mixture obtained was added dropwise under controlled magnetic stirring (at a temperature of 25 °C) to a solution of calcium acetate to obtain MPs of Fe [**35**,**36**]. The obtained particles were separated by filtration under vacuum and resuspended in distilled water to remove soluble salts, if any. This step was repeated to remove all the soluble salts. Finally, the particles were filtered under a vacuum to obtain Fe MPs. Thereafter, the MPs were dried at room temperature and subjected to further characterization studies or stored in a well-closed container with a small amount of talc till further use.

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**Table 1.** Composition of microencapsulated iron particles.

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### *2.3. Characterization of the Iron Microparticles*

#### 2.3.1. Optical Microscopy

The size of the Fe MPs was estimated using an optical microscope (Nikon Eclipse, E800, Tokyo, Japan). A small portion of the MPs (aggregate) along with a drop of water was placed on a slide and covered with a coverslip for microscopic examination using an optical microscope. The size was measured using a calibrated and superimposed scale on each image.

#### 2.3.2. Inductively Coupled Plasma Optical Emission Spectroscopy

The amount of calcium and iron in the Fe MPs was estimated using inductively coupled plasma optical emission spectroscopy (ICP-OES) (iCAP Pro, ICP-OES, Thermo Fisher Scientific, Waltham, MA, USA). A small portion (200 mg) of the MPs of Fe was combined with nitric acid and digested in a microwave oven and subjected to ICP-OES analysis.

#### 2.3.3. Scanning Electron Microscopy (SEM) with X-ray Energy Dispersion (EDS)

A high-resolution SEM (Carl Zeiss, Neon Crossbeam, Berlin, Germany) equipped with a spectrophotometer with an EDS (EDAX company, Unterschleissheim, Germany) was employed for the study. A voltage of 5 to 10 kV was employed as an acceleration voltage to obtain SEM images of the Fe MPs. A semi-quantitative detection was performed to detect the elemental composition of Fe MPs using an acceleration voltage of 10 kV.

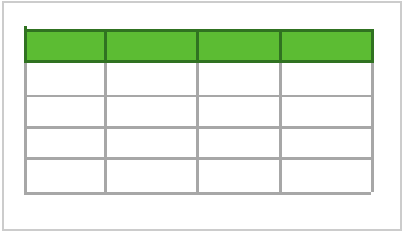
### *2.4. Fabrication of Pullulan-Based ODFs Loaded with Fe MPs*

A solvent casting method with minor modifications was employed to fabricate iron ODFs. **Table 2** lists the ingredients and quantities employed in the preparation. First, the film-forming polymer, pullulan, was dissolved in water and left overnight to obtain a clear solution. Similarly, lecithin was dissolved separately in a portion of the solvent. Fe MPs and beta-cyclodextrin were mixed in water under continuous stirring followed by the addition of mannitol and sweetening agents. Other ingredients,

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namely, calcium carboxymethylcellulose, ascorbic acid, and malic acid, were also added under continuous stirring for 15 min. Other excipients, namely, polyethylene glycol, sorbitol, and flavoring agents were then added under continuous stirring. Thereafter, the obtained solution along with the lecithin solution was added to the solution of pullulan under continuous stirring for about 20 min to obtain a homogenous slurry and subjected to deaeration under vacuum (pressure between 600 to 700 mm of Hg) for 2 to 3 h to remove air bubbles, if any. Finally, the solution was cast as a layer using an automatic layering machine with a predetermined thickness. Thereafter, the film is removed carefully and dried at a temperature of 60 °C followed by cutting and packaging in a tri-laminate aluminum pouch. The packed films are stored in a desiccator to prevent moisture or microbial attack and were used for further characterization.

**Table 2.** List of ingredients used for the preparation of iron orodispersible films (i-ODFs).



*2.5. Characterization of the ODFs*

2.5.1. Physical Examination

The fabricated pullulan-based i-ODFs were physically examined with respect to their appearance (using the naked eye), handling property, and texture.

2.5.2. Weight

The ODF samples were cut into a size of 2 × 2 $cm^2$ and weighed on an electronic balance (Mettler-Toledo, Mumbai, India). The average weight was considered as a mean weight variation.

2.5.3. Thickness

The thickness of the film was measured using a screw gauge having an accuracy of 0.001 mm. Measurements were taken from the center and also from the four corners of the film having the size of 2 × 2 $cm^2$. The thickness measured is reported as mean ± SD.

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### 2.5.4. Drug Content

To ensure the drug payload in the film, drug content analysis was done. A premeasured region of the film was dissolved in phosphate buffer (50 mL) by stirring followed by filtration through a filter paper (0.45 µm) and the amount of drug was determined by high-performance liquid chromatography (HPLC) method. The method employed a mobile phase comprising phosphate buffer (pH 2.5) and methanol in a ratio of 970:30 (flow rate: 1.0 mL/min). The detection wavelength was 210 nm and the run time was 15 min.

### 2.5.5. Disintegration Time

The disintegration time of the ODFs was measured by a Petri dish method [**37**], wherein a film of 2 × 2 $cm^2$ was placed in a Petri dish having 10 mL of phosphate buffer having pH of 6.8 (simulated salivary fluid; **Table S1**). The time taken for the ODF to disintegrate completely was measured using a stopwatch and the same experiment was repeated thrice and the mean value is reported.

### 2.5.6. Folding Endurance

The fabricated ODF was folded repeatedly at a predetermined spot until it broke. The number of times the film can be folded without breaking is taken as the value of folding endurance. The value was measured in triplicate.

### 2.5.7. Tensile Strength

To measure tensile strength, the ODF having a size of 2 × 2 $cm^2$ was clamped at one end and the other end was attached to a hanging pan for loading weights. The total weight required for the breakage of the film was estimated. The experiment was performed in triplicate and the tensile strength is reported as an average.

$$\text{Tensile Strength} = \frac{\text{Force at break (N)}}{\text{Initial area of the film } (\text{cm}^2)}$$

### 2.5.8. Surface pH

An ODF sample was moistened with distilled water (0.5 mL) and left for 2 min. The pH of the moistened film was measured using a pH meter (IKON Instruments, Delhi, India). In this method, the surface of the pH meter electrode was touched with the moistened surface of the film to measure the pH. Readings were taken in triplicate for each sample and the average value of the readings is reported.

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2.5.9. Karl–Fischer Titration (Water Content)

To determine the water content, Karl–Fisher titration was performed using a DL37 coulometric titrator (Mettler-Toledo, Mumbai, India). One ODF sample (2 × 2 $cm^2$) was added to about 5 mL methanol and the titration was continued until it reaches an electrometric endpoint. The water content determination was performed in triplicate corrected for solvent water content. The moisture content was calculated using the formula:

2.5.10. Morphology by Scanning Electron Microscopy (SEM)

The overall surface morphology of ODFs loaded with Fe MPs was evaluated by scanning electron microscopy (SEM) (Carl Zeiss, Neon Crossbeam, Berlin, Germany). The ODF sample (size: 1 $mm^2$) was positioned on a circular aluminum stub and sputter coated with Au/Pd under argon atmosphere using a vacuum evaporator followed by scanning using SEM.

2.5.11. Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectra (scanned between 4000 and 400 $cm^{-1}$; resolution: 4 $cm^{-1}$ for 20 scans) of the film-forming material, pullulan, ferric saccharate, iron-loaded microparticles, and the physical mixture for ODFs consisting of the active substance (iron) was carried out. The spectra were obtained by the traditional potassium bromide disc method followed by FTIR analysis (Shimadzu, model 8400, Tokyo, Japan) [**38**].

2.5.12. Microbial Load

The ODF samples were tested for microbial burden (aerobic colony count, molds, yeasts, and coliforms) as per ISO 11737-1 for determining the microbial load (population) in a product.

*2.6. Dissolution Studies*

An in vitro dissolution study of pullulan-based i-ODFs was performed in triplicate using a USP XXXIV paddle apparatus (type II) with 900 mL of 0.1 N HCl as dissolution media at 50 rpm and 37 ± 0.5 °C. Samples (aliquots of 5 mL) were collected periodically and replenished with equivalent volumes of fresh dissolution medium to maintain sink conditions. The collected samples were filtered through a filter paper (0.45 µm) and the amount of drug released was determined by high-performance liquid chromatography (HPLC) as aforementioned.

*2.7. Stability Studies*

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The optimized ODF formulation was subjected to stability studies at a temperature of 25 ± 2 °C and relative humidity of 60% ± 5% for 90 days. The ODFs were packed in a tri-laminate aluminum pouch and kept in a stability chamber. After the stipulated periods of 30, 60, and 90 days, the i-ODF samples were analyzed for their appearance (physical), thickness, drug content, folding endurance, surface pH, disintegration time (seconds), and dissolution profile.

*2.8. In Vivo Biocompatibility Study Using Hamster Cheek Pouch Model (Irritation Study)*

The mucosal irritation caused, if any, by i-ODF was assessed using a hamster cheek pouch model. This model was employed to study the safety of i-ODFs in the oral cavity. Hamsters of each sex were housed individually and provided with controlled environmental conditions of 12 h light/dark cycle with free access to both food and water. After acclimatizing for seven days, hamsters weighing between 100 to 150 g were selected for the study. The complete experimental procedures were carried out as per The Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) guidelines. The entire study was reviewed and approved by the Institutional Animal Ethics Committee (IAEC/JSSCPM/349/2020), Mysuru, Karnataka, India.

Study design: Hamsters were divided into two groups; Group I and Group II. Group I was kept on placebo film while Group II was kept on i-ODFs. Respective films were administered (positioned in the hamster's cheek pouch) for a time period of about 10 min followed by rinsing with distilled water. Thereafter, the pouch was immediately observed for redness (irritation), if any, and also after 24 h period. The placebo and i-ODFs were administered to hamsters twice a day for a time period of 4 to 5 days.

## 3. Results and Discussion

*3.1. Microencapsulated Iron Particles and Their Characterization*

Microencapsulation is a popular technology, wherein the active moiety is incorporated within a polymeric shell to prevent its interaction with the outside environment (other agents or oral mucosa) till it reaches the intestine. It also helps reduce the metallic taste in the oral cavity. Further, this technology offers protection against oxidation or heat, and thereby, enhances the shelf-life of the product. Sodium alginate is a natural polysaccharide consisting of β-D-mannuronic acid and α-l-glucuronic acid. When dissolved in water, it tends to form reticulated structures, wherein the anionic acid groups react with cations (divalent or polyvalent) to form an insoluble network. In the synthesis of Fe MPs, the viscous mixture of ferric saccharate and sodium alginate when introduced into the solution of calcium acetate forms an insoluble network by ionic cross-linking of the alginate, wherein the glucuronic acid portion of the alginate molecules forms junctions with calcium molecules, popularly called as egg-

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box [39]. Following this, the mixture was combined with β-cyclodextrin to undergo complexation. The host-guest interactions or linking between cyclodextrin with microencapsulated iron particles (**Figure 1**) help obtain a mixture that is ready for mixing with the solution of pullulan, the film-forming material.

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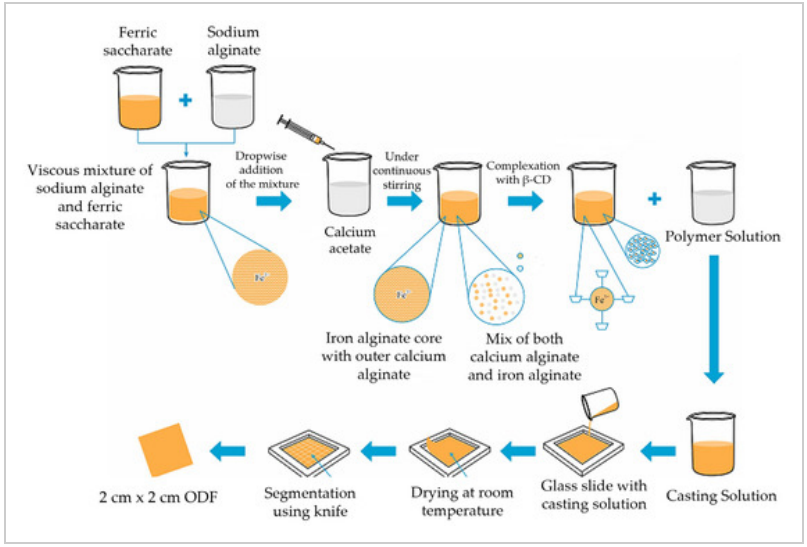



**Figure 1.** Schematic representation of preparation of iron-containing orodispersible films.

### *3.2. Characterization of Iron Microparticles*

Macroscopic aggregates were observed by the naked eye and these were very evident when seen under the microscope. The size of the aggregates ranged between 0.1 and 1 mm. Nonetheless, the size of the Fe MPs of Fe ranged from 5 to 15 µm, which is acceptable to proceed with the next steps of the fabrication process [**40**]. The amount of iron and calcium in batches P1 and P2 are expressed as a percentage of weight as shown in **Table 3**. From the results, it is evident that good iron loading capacity was observed in both batches.

**Table 3.** Concentration of iron and calcium in batches P1 and P2.

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Additionally, EDS analysis was performed on the Fe MPs and i-ODFs. The SEM images and EDS graph are represented in **Figure 2**. In addition, the weight percentages of different elements present in the Fe MPs and i-ODFs are summarized in **Table 4**. As depicted in **Table 4**, significant differences in the weight percentages of carbon and oxygen were observed between the Fe MPs and i-ODFs. Furthermore, the weight percentage of Fe in the microparticles was significantly higher than that in the orodispersible films. This is probably due to the complexation of Fe with β-CD in the film formulation. Other elements, namely, silicon and aluminum, are present in the Fe MPs but are absent in the film formulation.

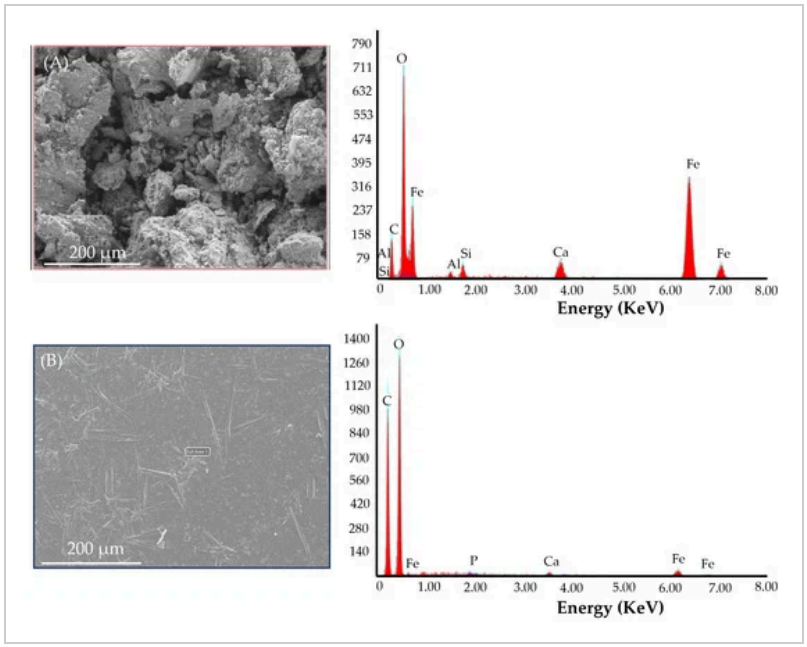
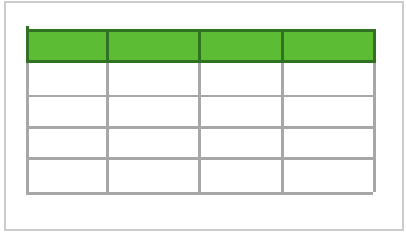



**Figure 2.** EDS analysis of (**A**) microparticles of iron and (**B**) pullulan-based iron-loaded orodispersible films.

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**Table 4.** Weight percentages of different elements in iron microparticles and pullulan-based orodispersible films of iron.

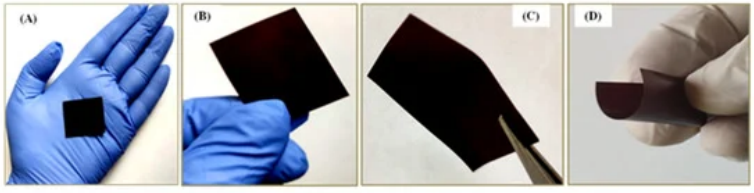




### *3.3. Iron Orodispersible Films (i-ODFs)*

Selection of Excipients

The oral delivery of drugs or nutrients using ODF technology is a relatively novel and inventive method. The solvent casting method stands out as the most preferred and industrially acceptable method for fabricating ODFs [**8**]. Different formulation batches (F1 to F6) were fabricated as summarized in **Table 2**. Glycerol, PEG 600, and sorbitol 70% were employed as plasticizers to help maintain the mechanical properties of the film. Lecithin and Tween 80 act as emulsifying agents to reduce the surface tension between the oily flavoring agents (such as kiwi and grape flavor) with the aqueous portion of the formulation. Some of the trial batches had problems such as the peeling of the film from the glass surface. To alleviate this issue, mannitol (5%) was employed as an anti-caking agent and helped in the smooth peeling of the film after casting from the glass surface. Ascorbic acid helps in enhancing the absorption of iron and malic acid helps stimulate the secretion of saliva in the oral cavity when the ODF is administered to the tongue. Calcium carboxymethyl cellulose is used as a disintegrating agent to facilitate rapid disintegration of the ODF when administered to the tongue. Different sweetening agents were employed in the formulation, namely, glucose, fructose, steviose 100, stevirome 5000, and steviol glycosides. The essential nutrients and pharmaceutically acceptable and compatible excipients used in the present study are listed in the United States Food and Drug Administration's list of Generally Recognized as Safe (GRAS) substances. The final optimized formulation (**Figure 3**) was subjected to further characterization to study the formulation properties and its stability.




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**Figure 3.** Pullulan-based iron-loaded orodispersible films (i-ODFs). (**A**,**B**) optimized formulation (F6) fabricated by modified solvent casting method; (**C**) side view of i-ODF showing thickness of the film; and (**D**) flexibility of the i-ODF.

### *3.4. Characterization of the Pullulan-Based Iron-Loaded Orodispersible Films*

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#### 3.4.1. Acceptability by the Subjects

As a quality criterion for acceptability by the subjects, the ODF must have a smooth texture and be free from air bubbles, flexible and soft to ensure excellent mouthfeel and good handling to gain patient acceptability and thereby compliance [**41**]. The ODFs of the present study when physically examined were found to be dark brown, free from air bubbles, flexible, and smooth textured, with moderate thickness. Formulation batches F5 and F6 were flexible, smooth, and thin, and thus were judged to be associated with good handling properties. Accordingly, they were assumed to possess good mouthfeel and thereby help in avoiding compliance issues from the subjects. Parameters such as disintegration time, mechanical properties, and moisture content were considered to be critical quality attributes that might affect the performance of the ODF [**42**,**43**]. Generally, ODFs should be easily portable (handling and transportation), rapidly disintegrate when administered to the tongue, and should have an allowable moisture limit to facilitate flexibility and must avoid tackiness. High moisture content can directly impact product stability (microbial and chemical) [**41**]. The results of desired evaluation parameters of different batches (F1 to F6) are shown in **Table 5**.

**Table 5.** Results of desired evaluation parameters of batches F1 to F6.

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#### 3.4.2. Weight Variation

The results obtained after measuring the weight are shown in **Table 5**. All the formulation batches exhibited narrow weight distributions with a low coefficient of variation. This parameter indicates uniformity in the distribution of the active essential

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nutrient, iron, in the pullulan-based ODF, as well as excipients. The weight of the pullulan-based iron ODFs ranged from 145 to 155 mg. The mean ± standard deviation weight of the 4 $cm^2$ ODF was 150 ± 5 mg, thereby signifying uniformity in the ODFs.

### 3.4.3. Thickness

Thickness is a physical property of the ODF that warrants uniformity in the casting process. The thickness results are tabulated in **Table 5**. The ODFs must neither be too thin to avoid handling issues nor too thick as it would have a direct impact on the disintegration time of the film. The optimized formulation batch (F6) exhibited an average thickness of 0.15 ± 0.01 mm. A small standard deviation indicates the uniformity in the ODFs and, therefore, the absence of drug islands or islands of undissolved substances in the film.

### 3.4.4. Folding Endurance (FE)

Folding endurance is a qualitative parameter that helps measure the mechanical strength such as brittleness or flexibility of the ODF. High FE indicates higher mechanical strength. The optimized formulation batches showed FE values ranging between 100 to 120 folds, indicating that the pullulan-based i-ODFs would be mechanically strong (not brittle in nature) during handling and while being administered to the tongue. In addition, the incorporation of the plasticizer combination (PEG 600 and sorbitol 70%) significantly enhanced the FE of pullulan-based i-ODFs (F6). Collectively, the film-forming polymer, pullulan, offered enough strength to the film and the plasticizer combination (PEG 600 and sorbitol 70% in a ratio of 2:4) exhibited flexibility in the optimized formulation batch (F6).

### 3.4.5. Surface pH

The surface pH of the pullulan-based iron ODFs ranged from 6.5 to 6.8, which was within acceptable limits. The ideal pH value must be close to 7.0 to avoid mucosal irritation in the oral cavity, thereby, helping in gaining patient compliance.

### 3.4.6. Disintegration Time

The Petri-dish method was adopted to determine the disintegration time of the ODF. The disintegration time of the pullulan-based iron i-ODFs in phosphate buffer (pH 6.8) was found to be below 25 s, thereby indicating rapid disintegration of the films. The complete disappearance of the disintegrated film into solution happened within 40 s. This is further indicated by the brown-colored solution (**Figure 4**).

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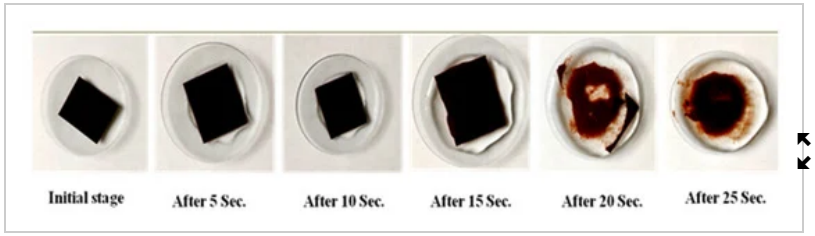





**Figure 4.** In vitro disintegration time of pullulan-based iron-loaded orodispersible films (i-ODFs) of batch F6 in phosphate buffer with a pH of 6.8.

### 3.4.7. Dissolution Profile

The iron-loaded ODFs administered to the tongue undergo rapid disintegration due to salivary hydration and are naturally swallowed along with saliva into the stomach via the esophagus. Absorption of iron occurs predominantly in the duodenum and upper jejunum. A variety of factors influence the absorption of iron, of which vitamin C (ascorbic acid) enhances iron uptake. In addition, the physical state of the iron entering the duodenum also plays a pivotal role in its absorption. Quick release of iron is vital for its absorption in the duodenum and upper jejunum. All the formulation batches showed a rapid release of iron from pullulan-based ODF (**Table 5**). It was observed that almost all batches showed Q5min of more than 90%. However, a few batches (F1 and F2) showed a Q5min of more than 85% but less than 90% due to a different plasticizer (glycerol + glycerol oleate) combination than the other batches (**Figure S1**). Therefore, from the dissolution study, it was evident that the combination of plasticizers (sorbitol 70% + PEG 600) with pullulan shows a better release profile.

### 3.4.8. FTIR Spectrophotometric Method

FTIR spectra of pure pullulan, ferric saccharate, the physical mixture of iron-loaded microparticles, and the final i-ODF are shown in **Figure 5**. In the spectra of pure pullulan, a sharp peak due to C=O stretching of both keto groups was observed at 1732 $cm^{-1}$. Similarly, in the spectra of ferric saccharate absorption bands are seen in the fingerprint region at 1033 $cm^{-1}$ due to C-O-C stretching vibration, at 1691 $cm^{-1}$ due to C=O five-membered cyclic stretching, and at 3427 $cm^{-1}$ due to aromatic N-H stretching vibration. Conversely, broad peaks were observed for the physical mixture of ferric saccharate at 1811 to 1957 $cm^{-1}$ and for the i-ODF between 1678 and 2158 $cm^{-1}$. The comparative spectra (**Figure 5**) clearly illustrate the absence of chemical interaction between pullulan and the excipients.

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**Figure 5.** Comparison of FTIR spectra of (**a**) pullulan, (**b**) ferric saccharate, (**c**) physical mixture of iron-loaded microparticles, and (**d**) iron-loaded orodispersible film (i-ODF).

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3.4.9. Morphological Study Using SEM

SEM studies were performed to examine the uniformity of the dispersion of ingredients in the pullulan-based i-ODFs. The analysis was carried out for sample A (iron-loaded pullulan-based ODFs without sweetening agents, and grape flavor) and sample B (iron-loaded pullulan-based ODFs with all the ingredients). The SEM images (**Figure 6**) show the difference between samples A and B. The surface of the ODF of sample A was rough/coarse when compared with the surface of sample B. This difference is primarily due to non-homogeneity in the dispersion of solids in the film-forming solution, pullulan, before casting the ODF. Accordingly, it can be inferred that good homogenization of all the ingredients is vital before casting the film to obtain an ODF with a smooth surface after the casting and drying steps. Most importantly, the SEM images (**Figure 6**) of the pullulan-based i-ODFs revealed good uniformity in the ODF. No aggregates were observed in the ODF, which could have formed during the drying process.

**Figure 6.** Micrographs by scanning electron microscopy (SEM) (**A**) images of sample A with rough surfaces and (**B**) images of sample B with smooth surfaces.

3.4.10. Tensile Strength

Tensile strength is another parameter used to characterize the mechanical properties of the ODF. It indicates how robust the ODF is to withstand stress during its journey from fabrication to handling by the end-user. In addition, a too-rigid film could cause a bad mouthfeel. A tensile strength of 165 ± 0.35 g/cm$^2$ was found to be optimum enough to offer the required toughness to the ODF to handle the stress experienced from fabrication to administration by the subject.

3.4.11. Karl–Fischer Titration

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The Karl–Fischer titration method helps determine the water content, if any, present in the pullulan-based i-ODF samples. Borges and colleagues recommended residual water content ranging between 3 to 6% *w/w* as ideal for the stability of an ODF [**35**]. The water content of the final formulation was found to range from 4.0 to 5.0% *w/w*. Therefore, this value indicates good physical stability and integrity of the ODF.

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3.4.12. Microbial Bioburden

The microencapsulated iron ODF samples were tested for the presence of microorganisms by in-house standard testing procedures. The test procedure involves testing the samples for the presence of microorganisms, namely, yeast and molds, *E. coli* (bacteria), *Staphylococcus aureus*, and *Pseudomonas aeruginosa*. Except for yeast and molds (with <10 CFU/g), the remaining microorganisms were absent. Accordingly, the formulated ODFs were found to be within the pharmaceutically acceptable criteria (total aerobic count: $<10^3$ CFU/g and total yeast and molds $<10^2$ CFU/g) from the microbiological point of view for non-sterile dosage forms [**44**].

3.4.13. Drug Content

The iron content in the sample ODF, as determined by HPLC, was found to be 99.4% of the label claim (27 mg per each strip of ODF) as the average value for the optimized formulation.

*3.5. Stability Studies*

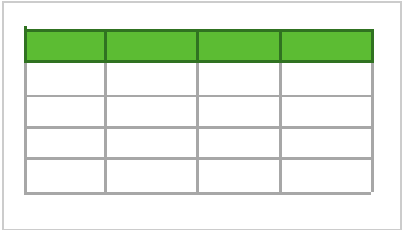
Stability studies were performed for the optimized i-ODF formulation (F6) by investigating the visual appearance, thickness, drug content, folding endurance, surface pH, disintegration time (seconds), and dissolution profile after a period of 30, 60, and 90 days, and the results are summarized in **Table 6**. The study results confirmed a lack of any significant variation in the desired properties of the film formulation such as surface thickness, pH, disintegration time, appearance, folding endurance, and drug content over three months when packed and stored in the tri-laminate aluminum pouch (**Figure 7**) at 25 ± 2 °C and a relative humidity of 60% ± 5%. Most importantly, the iron content in the ODF after 90 days was found to be 98.51 ± 0.45%. Accordingly, the pullulan-based i-ODFs were found to be stable for 90 days when stored in a tri-laminate aluminum pouch. Therefore, the tri-laminate aluminum pouch is considered ideal for packaging and storing pullulan-based i-ODFs.

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**Figure 7.** Tri-laminate aluminum pouch for packaging iron orodispersible films (i-ODFs): (**A**) Front view of the pouch with pictorial instructions to open and consume i-ODF and (**B**) Back view showing directions to open (**C**) single pullulan-based i-ODF per pouch in an open position (**D**) i-ODF removed after stability studies.

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**Table 6.** Stability data of the optimized i-ODF formulation F6 (*n* = 3).



*3.6. In Vivo Biocompatibility Study Using Hamster Cheek Pouch Model (Irritation Study)*

Generally, the formulated i-ODFs when administered to the tongue tend to come in contact with oral mucosa. Therefore, biocompatibility studies of i-ODFs are a prerequisite to clinical use. The hamster cheek pouch model [**9**] was found to be an appropriate model to test the irritation of i-ODFs, if any, when administered via the oral route. Based on macroscopic observations, no redness (irritation) was observed on the cheek pouch area of hamsters both before and after placing i-ODFs. Accordingly, the fabricated pullulan-based i-ODFs were deemed free from irritation.

## 4. Conclusions

Taste-masked pullulan-based i-ODFs were successfully fabricated by a solvent-casting method. The optimized batch (F6) exhibited excellent disintegration time, good folding endurance, a high percentage of drug release, and good stability when stored in a tri-laminate aluminum pouch. In addition, the incorporation of mannitol in all the formulation batches helped in acting as an anti-caking agent and facilitated the peeling of the film from the smooth casting surface, which in turn, might enhance acceptability by the subjects. Most importantly, the film is free from irritation when administered to the tongue as confirmed by a hamster cheek pouch model and surface pH determination (pH = 6.5 to 6.8). In summary, the film-forming agent, pullulan, was successfully employed on a lab scale to formulate orodispersible films of iron. Furthermore, the ODFs of the present study can be processed easily on a large scale and can be commercialized successfully.

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## Supplementary Materials

The following supporting information can be downloaded at: **https://www.mdpi.com/article/10.3390/pharmaceutics15031027/s1 (https://www.mdpi.com/article/10.3390/pharmaceutics15031027/s1)**, Figure S1: Dissolution rate of pullulan-based i-ODFs; Table S1: Composition of Simulated Salivary Fluid (SSF; pH 6.8).

## Author Contributions

Conceptualization, T.P.K. and D.V.G.; methodology, M.S.G., T.P.K., D.R., K.P. and A.V.N.B.; software, A.S.A.L., E.-S.K., A.M. and T.H.; validation, T.P.K. and D.V.G.; formal analysis, A.M., T.H., A.H.A. and H.F.A.; investigation, M.S.G., T.P.K., D.R., K.P. and A.V.N.B.; resources, A.H.A. and H.F.A.; data curation, A.S.A.L., E.-S.K., A.M. and T.H.; writing—original draft preparation, M.S.G., T.P.K., D.R., K.P. and A.V.N.B.; writing—review and editing, A.S.A.L. and A.H.A.; supervision, T.P.K. and D.V.G.; funding acquisition, A.H.A. and H.F.A. All authors have read and agreed to the published version of the manuscript.

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## Institutional Review Board Statement

The animal study protocol was approved by the Institutional Animal Ethics Committee (IAEC/JSSCPM/349/2020), Mysuru, Karnataka, India.

## Informed Consent Statement

Not applicable.

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## Data Availability Statement

Not applicable.

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## Conflicts of Interest

The authors declare no conflict of interest. Aavishkar Oral Strips Private Limited had no role in the design of the study.

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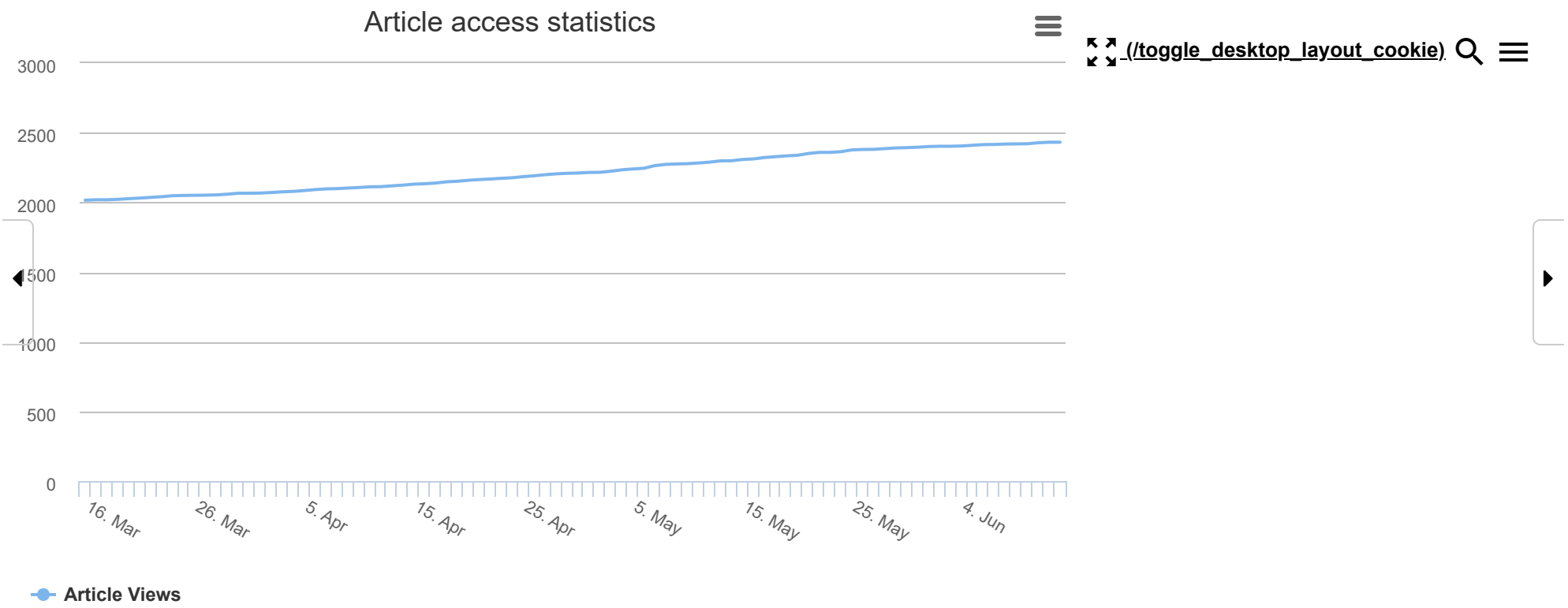
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# Amelioration of Cancer Employing Chitosan, Its Derivatives, and Chitosan-Based Nanoparticles: Recent Updates

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## Abstract

The limitations associated with the conventional treatment of cancer have necessitated the design and development of novel drug delivery systems based mainly on nanotechnology. These novel drug delivery systems include various kinds of nanoparticles, such as polymeric nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, hydrogels, and polymeric micelles. Among the various kinds of novel drug delivery systems, chitosan-based nanoparticles have attracted the attention of researchers to treat cancer. Chitosan is a polycationic polymer generated from chitin with various characteristics such as biocompatibility, biodegradability, non-toxicity, and mucoadhesiveness, making it an ideal polymer to fabricate drug delivery systems. However, chitosan is poorly soluble in water and soluble in acidic aqueous solutions. Furthermore, owing to the presence of reactive amino groups, chitosan can be chemically modified to improve its physiochemical properties. Chitosan and its modified derivatives can be employed to fabricate nanoparticles, which are used most frequently in the pharmaceutical sector due to their possession of various characteristics such as nanosize, appropriate pharmacokinetic and pharmacodynamic properties, non-immunogenicity, improved stability, and improved drug loading capacity. Furthermore, it is capable of delivering nucleic acids, chemotherapeutic medicines, and bioactives using modified chitosan. Chitosan and its modified derivative-based nanoparticles can be targeted to specific cancer sites via active and passive mechanisms. Based on chitosan drug delivery systems, many anticancer drugs now have better effectiveness, potency, cytotoxicity, or biocompatibility. The characteristics of chitosan and its chemically tailored derivatives, as well as their use in cancer therapy, will be examined in this review.

**Keywords: chitosan (/search?q=chitosan)**; **modified chitosan (/search?q=modified+chitosan)**; **biopolymer (/search?q=biopolymer)**; **chitosan nanoparticles (/search?q=chitosan+nanoparticles)**; **cancer (/search?q=cancer)**; **patent (/search?q=patent)**; **co-delivery (/search?q=co-delivery)**

## 1. Introduction

Cancer is the most confounding illness of the 21st century and is growing enormously without any discernment based on cell type, age, or gender [**1**]. Although incredible advancements in cancer treatment have been achieved, the prevalence and mortality rates are still the highest across the world. The World Health Organization estimated that 10 million deaths in 2020 were credited to cancer, and 400,000 children are diagnosed with cancer annually. It is anticipated that there will be 29.5 million

new cases and 16.4 million cancer-related deaths by 2040, which is a serious health burden around the globe [**2**]. An additional fact is that about one in six deaths is attributed to cancer across the globe. This exceedingly endemic disease is currently estimated to be the second most prevalent cause of mortality after cardiovascular diseases [**3**]. Approximately 70% of cancer deaths belong to low and middle-income nations, depicting a significant impact on low and middle-income nations both physically and economically [**4**]. However, making little lifestyle changes, abstaining from drinking, and quitting chewing tobacco can lower cancer cases by around 30% to 50% [**5**].

The treatment of cancer is challenging and necessitates a combination of several parallel and subsequent therapies, such as surgery with chemotherapy and surgery with radiotherapy, depending on the type and stage of the cancer. Although chemotherapy is mainly employed to treat cancer, there are various alternative treatment options for cancer, as depicted in **Figure 1**.




**Figure 1.** Various treatment modalities for the management of cancer.

The Food and Drug Administration (FDA) has permitted the use of more than 300 chemotherapeutic agents to treat cancer. But the heterogeneous nature of cancer has limited the efficacy of all these chemotherapeutic agents [**6**]. These agents encounter several difficulties, such as drug-related adverse effects, drug resistance, the insensitivity of cancer cells to treatments, and a lack of drug targeting [**7**,**8**]. In addition, more crucially, some of the key downsides of chemotherapeutic agents include the need for high doses, poor absorption, a low selectivity index, non-specific interactions, and patient

discomfort [**9**,**10**]. Furthermore, chemotherapeutic agents demonstrate their effectiveness in treating cancer by specifically targeting cell proteins, nucleic acids, and carcinogenic signaling pathways that drive cancerous cells to adapt to changes in their environment and promote the spread of cancer [**8**]. Therefore, it is necessary to look for novel and advanced treatment alternatives for boosting the therapeutic efficiency of chemotherapeutic agents.

Advanced treatment options involve the nanotechnology approach, a rapidly evolving cutting-edge scientific area that integrates a variety of fields like chemistry, physics, and biology, as well as the creation of novel nano-dimension structures with therapeutic uses in pharmacology and the biomedical industry [**11**,**12**]. Numerous characteristics of the nanodimension, including optical, magnetic, and structural surface area ratios, make it an exciting subject for research in every way [**13**,**14**]. Due to the increased surface area of nanoscale medicines or devices, they serve as nanocarriers and nanoadsorbents and transport therapeutic substances, proteins, or probes [**15**,**16**]. These nanoscale methods comprise solid lipid nanoparticles (SLNs), liposomes, nanostructured lipid carriers (NLCs), nanoemulsions (NEs), polymeric nanoparticles (PNPs), polymeric micelles (PMs), carbon nanotubes (CNTs), and dendrimers [**17**,**18**]. Among the numerous kinds of nanocarriers, polymeric nanoparticles (PNPs) have been widely exploited for the delivery of anticancer drugs owing to various characteristics such as biodegradability, biocompatibility, reduced size, amplified surface volume ratio, and easier reformation of structure and surface [**19**] PNPs enable the protection of enveloping drug molecules and control or sustain the release of embedded drugs. The potential of PNPs to transport chemotherapeutic agents is unremittingly growing due to their capability to target the chemotherapeutic agents only on cancer cells [**20**]. Numerous polymers have been employed for the fabrication of PNPs, which include natural (cellulose, chitosan, gelatin, lysozyme, dextran, collagen, and albumin), synthetic (poly lactide-co-glycolide (PLGA), polylactic acid (PLA), thiolated poly methacrylic acid), and semisynthetic (methylcellulose) polymers [**21**].

Natural polymers have received a great deal of attention for the fabrication of PNPs for the delivery of anticancer drugs due to their possession of numerous characteristics: higher biocompatibility, biodegradability, interactions with biomolecules, controlled enzyme degradation, low immunogenicity, ease of surface modification, and economics [**22**,**23**]. Amongst these natural polymers, chitosan has received the courtesy of researchers as a drug delivery system to deliver chemotherapeutic agents due to distinct characteristics like great drug loading capability, sustained circulation capacity, multifunctionality, drug release at cancerous sites in an efficient manner, removal of cytotoxicity to non-cancerous cells, auspicious targeting, and permeability of cell membranes owing to the presence of a primary amine group in their chemical structure [**24**,**25**]. Chitosan provides specific targeting to cancerous cells due to functionalization with various specific polymers such as hyaluronic acid (HA), polyethylene glycol (PEG), folic acid (FA), RGD, etc. In a study, Almutairi FM et al. prepared hyaluronic acid-decorated

chitosan nanoparticles loaded with raloxifene to treat lung cancer and found that raloxifene-hyaluronic acid-chitosan (RX-HA-CS) nanoparticles exhibited greater cytotoxicity against A549 cancer cells than raloxifene-hyaluronic acid (RX-HA) nanoparticles and raloxifene-chitosan (RX-CS) nanoparticles. This noteworthy dominance of A549 cell viability was attained through glucose uptake lessening, which resulted in reduced bioenergetics of cancer cells and stimulation of apoptosis through nitric oxide level elevation [**26**]. In another study, Ullah et al. prepared folic acid-decorated chitosan nanoparticles embedded with 5-fluorouracil and investigated whether cytotoxic potential was improved in the presence of folic acid. The folic acid-decorated chitosan nanoparticles showed greater cytotoxicity than plain, undecorated chitosan nanoparticles in colon cancer [**27**]. This depicts that functionalization of chitosan nanoparticles with specific molecules improves the site-specific potential of drug molecules embedded in them. The chemical structure of chitosan and its properties as an ideal drug delivery system are depicted in **Figure 2**.

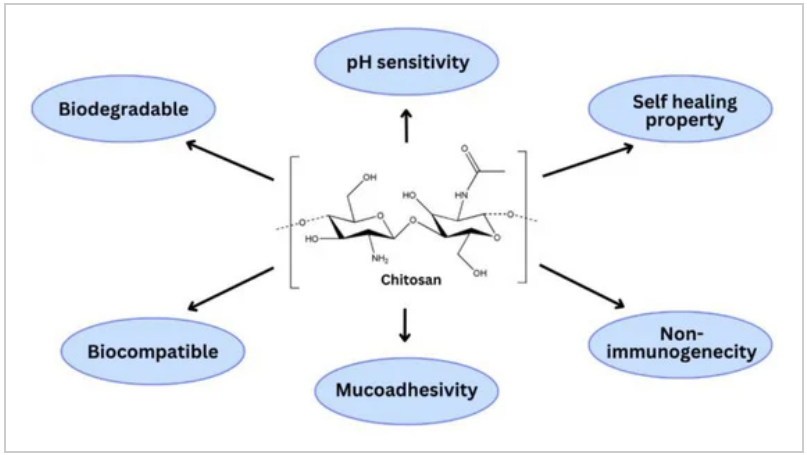


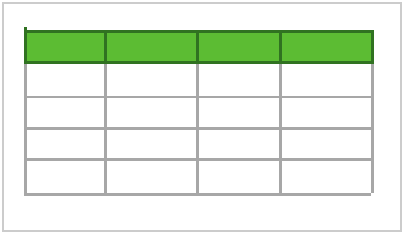

**Figure 2.** Chemical structure of chitosan along with model pharmaceutical properties.

## 2. Conventional Chemotherapeutic Treatment

Chemotherapy is perceived to be the most successful form of treatment for cancer since it specifically targets cancerous cells and kills them, preventing their spread or decreasing their growth [**24**]. Chemotherapy has a long history that dates back to the early 20th century, but its use to treat cancer was started in the 1930s. The word “chemotherapy” was created by the German scientist Paul Ehrlich to refer to the use of chemicals to cure the disease [**28**]. Ehrlich had a keen interest in alkylating

agents. It was discovered that soldiers exposed to mustard gas during the First and Second World Wars had lower numbers of leukocytes. As a result, Gilman utilized nitrogen mustard as the first chemotherapeutic drug to treat lymphomas in 1943. Alkylating agents for the treatment of cancer, such as cyclophosphamide and chlorambucil, were created in the years that followed [**29**]. Thus, progress in chemotherapeutic agents ensued, and some anticancer drugs were developed. Various chemotherapeutic agents employed in the treatment of cancer have been summarized in **Table 1**.

**Table 1.** A compilation of traditional chemotherapeutic agents [**8**].



Some of the drugs like vincristine, vinblastine, and paclitaxel listed in **Table 1** are of plant origin, which has prompted scientists to search for more plant-derived drugs. Numerous studies have focused on plant-derived agents' medicinal properties, which are now widely used for the treatment of various kinds of ailments, especially cancer [**3**]. The focus on plant-derived agents for the treatment of cancer is attributed to various characteristics such as low adverse effects, action via several paths, and low cost therapy [**30**,**31**]. Some plant-derived anticancer drugs having great anticancer potential include paclitaxel, beta-lapachone, lapachol, colchicine, curcumin, resveratrol, quercetin, naringin, allicin, piperine, epigallocatechin, andrographispaniculata, glinuslotoides, saussurealappa, punicagranatum, betulinic acid, and ashwagandha [**8**,**32**]. These plant-derived anticancer agents owe their anticancer properties to numerous mechanisms like the prevention of cancer cell-triggering proteins, enzymes such as topoisomerase, cyclooxygenase, CDK4 kinase, CDK2, Cdc2, MAPK/ERK, MMP, initiation of DNA repair mechanisms, signaling pathways, stimulation of antioxidant action, or prompting of the development of protective enzymes (Caspase-3, 7, 8, 9, 10, 12) [**33**].

## 3. Obstacles Associated with Conventional Chemotherapeutic Agents

The therapeutic efficacy of the chemotherapeutic agents available to treat cancer is limited for some reasons, including their non-specific nature, countless adverse effects, higher dose requirements, short half-lives, widespread biological

distribution, drug resistance, drug instability, poor aqueous solubility, low bioavailability, and lack of drug targeting [**34**,**35**]. These chemotherapeutic agents are unable to differentiate between cancerous cells and non-cancerous cells, resulting in the destruction of normal cells and the initiation of serious toxic effects that are lethal [**36**]. Some of the frequently reported toxic effects include low blood counts, exhaustion, mouth discomfort, nausea, vomiting, loss of appetite, constipation or diarrhea, hair loss, skin changes or responses, pain or nerve alterations, and reduced fertility and sexuality [**37**]. Rarely, chronic use of conventional chemotherapeutic agents may cause the emergence of secondary cancer [**24**].

However, the extremely broad range of toxic effects reported strongly suggests that the foremost challenge in chemotherapeutic agent-based cancer treatment resides in the targeting stage of these agents, or more specifically, in the successful transport and distribution of these agents in the body [**38**]. They do not appear to get to the intended cancer cell, and they do not seem to get there intact either. As a result, a chemotherapeutic agent spreads freely throughout the body, which is why side effects occur. This is the fundamental reason why, even though various chemotherapeutic agents are quite effective at eliminating or killing cancer cells in laboratories, they have fallen short of demonstrating progressive improvement when used on humans [**24**]. Targeted drug delivery and controlled drug release thus stand out as one of the most significant and promising approaches to enhancing the effectiveness of chemotherapeutic agents, which in laboratory settings demonstrate substantial efficacy while significantly decreasing the toxic effects [**39**,**40**]. Hence, there are mainly two obstacles to the effective treatment of cancer using chemotherapeutic agents: the inability to stop the agent from interacting with healthy non-cancerous cells, especially when it is in free form, and the delivery of the agent to the tumor site properly. This has resulted in the development of novel drug carriers such as liposomes, SLNs, NLCs, polymeric micelles, NEs, nanosuspensions, quantum dots, CNTs, and dendrimers.

PNPs have emerged as crucial targets for delivering chemotherapeutic agents to cancerous cells owing to their unique attributes [**41**]. The trademark qualities of PNPs as cancer drug delivery systems, including controlled drug release, targeted drug delivery, increased therapeutic efficacy, and safety, have been demonstrated in numerous studies [**42**,**43**]. Due to the attachment of targeting ligands to the surface of PNPs, they are frequently used as drug delivery systems for chemotherapeutic agents. The controlled release of loaded chemotherapeutic agents is made possible by the surface modification of these PNPs with targeting ligands, which allows recognition by particular receptors or ligand binding sites that are overexpressed on cancer cells or at target areas [**44**,**45**]. In addition, to prevent the PNPs from being phagocytosed and opsonized by circulating phagocytic cells, hydrophilic chains might be added to their exterior. PNPs can be fabricated using synthetic (poly lactide-co-glycolide (PLGA), poly (ε-caprolactone) (PCL), polylactic acid (PLA), semi-synthetic (methylcellulose), and natural (lysozyme,

gelatin, cellulose, dextran, chitosan, collagen, and albumin) polymers [**8**]. Natural polymers have received a great deal of attention for the fabrication of PNPs for the delivery of chemotherapeutic agents due to their higher biocompatibility, biodegradability, interactions with biomolecules, controlled enzyme degradation, low immunogenicity, ease of surface modification, and economics [**22**].

## 4. Chitosan and Its Derivatives for Anticancer Drug Delivery

Chitosan is a versatile polycationic, linear natural polysaccharide composed of N-acetyl-β-(1-4)-D-glucosamine and β-(1-4)-D-glucosamine units and originated from chitin employing the process of deacetylation [**46**]. Chitosan has drawn distinct attention as a drug delivery system because of its superior chemical and biological characteristics. Owing to its polycationic makeup, chitosan is a bioadhesive polymer that rapidly adheres to negatively charged surfaces like mucosal membranes. In this manner, it strengthens the adherence to the mucosal surfaces, thereby lengthening the duration that drug molecules are in contact with them [**47**]. The complex characteristics of chitosan facilitate the delivery of anionic drugs, low molecular weight drugs, and polyanionic compounds like SiRNA and DNA [**48**]. Chitosan possesses a positive charge, and cyclodextrin has a negative charge. The gelation of chitosan with cyclodextrin provides a modified chitosan drug carrier with the capability to carry hydrophilic as well as hydrophobic drugs. Cyclodextrin has a truncated cone structure with a hydrophilic outer surface and a hydrophobic interior cavity. As a result of hydrophobic interactions, a variety of lipophilic drugs can be loaded into the hydrophobic cavity of *β*-cyclodextrin, leading to improved solubility, loading efficiency, and stability of lipophilic drugs [**49**]. The drug-carrying capacity of chitosan increases with an increase in charge, which shows its ability to act as a pH-dependent drug carrier [**50**].

Chitosan also possesses permeation enhancement property which depends upon the positive charge of the polymer. Chitosan, having a high molecular weight and a great degree of deacetylation, provides improved epithelial permeability and hence causes the passage of polar drugs through epithelial surfaces [**51**]. It has better biocompatibility and poor toxicity. It is a biodegradable polymer that breaks down into harmless compounds that are fully absorbed by the body [**52**]. It also possesses efflux pump inhibitory properties due to which it blocks certain transporter proteins on the membrane of intestinal epithelial cells or enterocytes that release xenobiotics, primarily drugs, making these transporters one of the key elements of drug resistance mechanisms [**53**]. The presence of hydroxyl and amino groups in their structure provides prominent properties like pH sensitivity, gelation capability, improved permeability, and antimicrobial activity, which possess significant consequences for

controlled drug release and targeted drug delivery [**54**,**55**]. These incredibly alluring qualities have increased interest in chitosan and its derivatives in recent years, leading to the development of safe and effective drug or gene carriers for cancer-targeted delivery systems.

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The properties of chitosan can be modified by employing physical and chemical modifications of the hydroxyl groups and free amino groups present in its structure [**56**]. Due to the presence of ridiculous functional groups, namely the amino group, primary hydroxyl, and secondary hydroxyl group at C-2, C-3, and C-6 positions, respectively, the parent structure of chitosan can be modified through acylation, alkylation, esterification, etc. to get modified chitosan derivatives having desirable physical, chemical, and biological characteristics, as depicted in **Figure 3** [**57**].

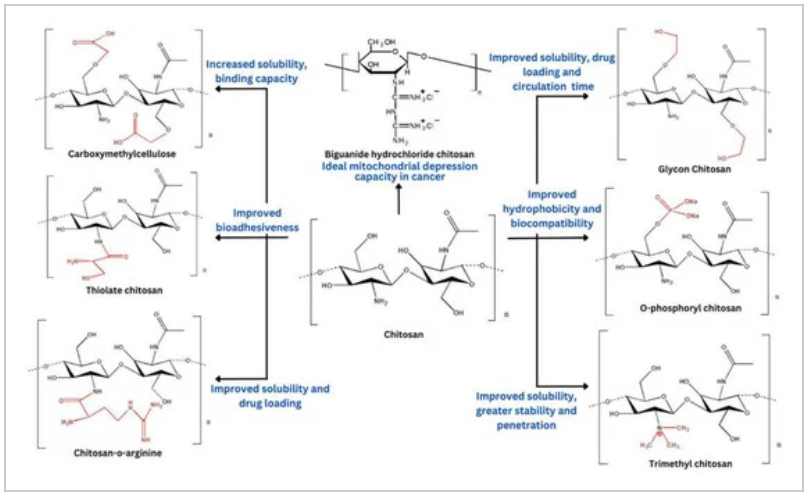



**Figure 3.** Modified chitosan along with their characteristics for improved drug delivery.

By providing modifications in molecular weight, crosslinking, degree of deacetylation (DD), functional groups and moieties, synchronized anions or polyanions, etc., the modified chitosan has improved properties [**50**]. For instance, the solubility of chitosan can be significantly increased by adding tiny chemical groups like hydroxypropyl or carboxymethyl groups to its structure [**58**]. To introduce an anionic character with water-soluble properties, superior paste fluidity, a high water-reducing ratio, and anticoagulant properties, the cationic property can be reversed via sulfonation. With an increase in the crosslinking of chitosan, the mechanical strength of particles also increases [**59**]. Particles with a high degree of crosslinking exhibit decreased

swelling, inner water infiltration, and outside drug diffusion. Drug release can be slowed by crosslinking, and burst releases can be avoided [**60**].

The mucoadhesive characteristic of chitosan can be enhanced by employing trimethylation of the primary amino group, PEGylation, or immobilization of the thiol groups present in its structure [**61**]. Amino groups in the structure of chitosan provide cationic properties, which are responsible for its solubility. This weak base is only soluble in diluted acidic solutions and insoluble in water and organic solvents because of the protonation of amine groups [**62**]. The higher amino group counts result in decreased molecular weight and improved solubility.

The viscosity of chitosan rises with a rise in molecular weight. Because hydrogen interactions across chains have a greater impact as molecular weight increases, solubility decreases [**63**]. The limited aqueous solubility restricts its application, whereas its solubility in acidic pH provides an opportunity to explore chitosan [**64**]. The reactive amine and hydroxyl functional groups of this biopolymer also render it vulnerable to chemical modification to enhance or acquire new features. To get around this obstacle, several derivatives of chitosan have been developed, which has multiplied its uses in the field of biomedicine for the delivery of active pharmaceutical ingredients by means of chemotherapy, immunotherapy, phytotherapy, and gene therapy [**65**]. At present, numerous drug delivery systems, namely microspheres, films, particles, nanofibers, nanocapsules, and nanocomposites, have been developed employing chitosan, which can be administered within the body via various routes like oral, intravenous, topical, nasal, and ocular routes [**66**].

Some immune checkpoints, such as Sting and CTLA-4, and programmed death-ligand 1 (PD-L1), are also affected by chitosan and its derivatives. Chitosan and its derivatives cause activation of the mitochondrial DNA-mediated cGAS-STING (Cyclic GMP-AMP synthase-Stimulator of Interferon Genes) pathway followed by the release of type I interferon, resulting in the immunostimulatory effect of chitosan [**67**]. Oral PD-L1 Binding Peptide 1 (OPBP-1), a proteolysis-resistant oral PDL-1 inhibitor that could specifically bind PD-L1 and disrupt its interaction with PD-1, was created using trimethyl chitosan. When loaded with trimethyl chitosan hydrogel, OPBP-1 demonstrated favorable oral bioavailability and a long half-life in rats and dramatically reduced tumor growth in mouse colorectal CT26 and melanoma B16-OVA models [**68**]. Cytotoxic T-lymphocyte antigen 4 (CTLA-4) molecules are one of the main barriers to priming T cells by dendritic cells (DCs). Therefore, it seems that blockade of such molecules facilitates T cell activation. In a study, suppression of the expression of the CTLA-4 molecule on tumor-infiltrating T cells by siRNA-loaded chitosan-lactate (CL) nanoparticles was facilitated [**69**].

## 5. Chitosan Nanoparticles as Anticancer Drug Delivery System

Considering the excellent characteristics of chitosan, the use of chitosan nanoparticles (CSNPs) has been exploited for the delivery of chemotherapeutic agents in the treatment of cancer. CSNPs provide various benefits, including ease of manufacturing, biocompatibility, biodegradability, mucoadhesiveness, improved permeation, economics, and ecofriendliness. The presence of cationic functional moieties and the electrostatic interaction of chitosan with various chemotherapeutic agents have provided it with excellent characteristics for efficient drug delivery in cancer [**65**]. Furthermore, CSNPs possess outstanding properties such as the ability to adjust the pharmacodynamic and pharmacokinetic of the drugs, the capability to transport both hydrophobic and hydrophilic drugs, controlled and sustained drug release, rapid penetration from biological membranes, increased accumulation of drugs in the internal environment of the diseased site, low immunogenicity, sustainability, and the capability of surface modification owing to the presence of amine and hydroxyl groups [**70**]. The transport of lipophilic drugs by CSNPs is possible by modification with specific molecules like cyclodextrin and hyaluronic acid. This modification of chitosan having a positive charge with hyaluronic acid or cylcodextrin having a negative charge via ionic interaction provides modified nanoparticles having the capability to carry lipophilic drugs [**71**]. In addition, CSNPs have good mechanical properties and thermal stability and can be modulated in different forms like powders, films, hydrogels, and porous frameworks [**72**]. CSNPs can also bypass the tight junctions present in epithelial cells [**73**]. The mucoadhesive property of CSNPs enables increased retention time at specific sites, enabling an increase in the therapeutic effectiveness of the drugs [**74**]. Based on their physicochemical characteristics, CSNPs employed for the loading of chemotherapeutic agents can be fabricated using a variety of techniques. The most practical and widely described methods include electrostatic adsorption, ionic gelation, covalent cross-linking, and self-assembly. Additionally, there are other methods for creating chitosan-based nanoparticles, including electrospinning, emulsification, and solvent evaporation [**70**,**75**].

To provide effective cancer drug therapy, it is necessary to target the chemotherapeutic agents at the cancer site. The drug targeting of cancer sites can be accompanied by two mechanisms, namely passive targeting and active targeting [**76**] as depicted in **Figure 4**.

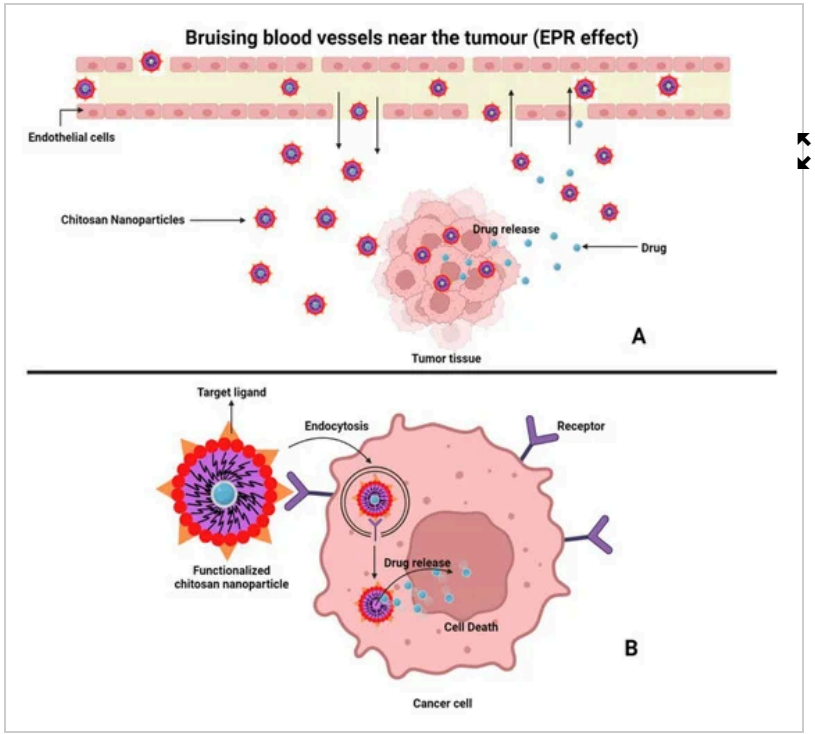



**Figure 4.** Representation of associated mechanisms for drug targeting to cancer site; Active targeting (**A**), Passive targeting (**B**).

In passive drug targeting, the CSNPs are transported to the cancer site using leaky tumor capillary penetrations. The enhanced permeability and retention (EPR) effect is then used to selectively transport drug-embedded nanoparticles into cancer cells. This is crucial for the uptake of CSNPs into cancer cells, especially in rapidly developing solid tumors. The ability of CSNPs to internalize into cancer cells can be increased by up to 50 times more than it is in normal cells [**77**]. These high ratios result from extensive angiogenesis with vascularization, irregular blood vessel structure between endothelial cells, damaged lymphatic drainage systems, rapidly proliferating tumor tissues, the absence of a smooth muscle layer in cancer blood vessels, the slow venous return of nanoparticles from the tumor environment, and the need for a higher oxygen supply to support rapid tumor proliferation [**78**].

CSNPs can potentially build up in cancer cells for a prolonged time owing to incomplete venous and lymphatic drainage. Furthermore, the mucoadhesive characteristics and the capacity to pass through momentarily open epithelial tight junctions

might enhance the distribution of drugs across a variety of well-organized epithelia, including ophthalmic, oral, pulmonary, intestinal, etc [**79**]. However, several CSNP characteristics like size, shape, and surface characteristics may have a significant impact on the passive accumulation of nanoparticles in cancer regions because they have an impact on how nanoparticles are administered, distributed, metabolized, and eliminated. Because of the opsonic effect, CSNPs larger than 200 nm in diameter, non-globular in shape, and lacking biocompatible surfaces can be removed from human body serum with ease, while those smaller than 200 nm can significantly escape from the opsonic effect and offer a longer blood circulation time [**80**,**81**]. The uptake of nanoparticles in cells is influenced by their size and shape. Nanoparticles' physical and chemical properties, such as size, shape, surface charge, and composition, influence how cells internalize them. Endocytic macrophages will expand to any size greater than 200 nm, aided by the addition of a ligand like folic acid or an epithelial protein. It is common knowledge that size is significant. In earlier investigations, smaller NPs were more likely to enter cells through endocytosis or diffusion, while larger NPs were more likely to enter cells through phagocytosis [**82**]. Surface modifications with different biomolecules, such as polyethene glycol, polylactic acid, and polylactic-co-glycolic acid, can significantly increase the physical stability and blood circulation time of CSNPs by evading the immune system and reticuloendothelial system [**83**]. The development and usage of metformin-modified chitosan could provide sensitization to the chemotherapy efficiency of cis-platinum due to its ideal capacity for selective mitochondrial accumulation, which further disrupted mitochondrial function. This, in turn, prevented the upregulation of programmed cell death ligand 1 (PD-L1) to prevent DNA damage repair in tumor cells, as well as decreased drug efflux and tumor metastasis [**84**]. Another chitosan derivative, biguanide-modified chitosan, had the greatest ability for mitochondrial depression, resulting in a reduction in the dosage required to interfere with mitochondrial function, reverse tumor hypoxia, and suppress MDR-1 expression [**85**]. Chitosan oligosaccharide (COS) might prevent the increased PD-L1 expression through the activation of AMPK and suppression of Signal Transducer and Activator of Transcription 1(STAT1) brought on by interferon (IFN) in a variety of tumors. Furthermore, COS itself dramatically inhibited CT26 tumor growth by promoting T cell infiltration in tumors. Additionally, we saw that adding COS to the common chemotherapy medication Gemcitabine (GEM) resulted in a more notable tumor remission [**86**].

Chitosan and its derivatives improve the sensitivity of other tumor therapies such as chemotherapy, radiotherapy, phototherapy, and chemoradiotherapy (CRT). Chitosan oligosaccharide may inhibit the abnormally up-regulated programmed cell death ligand 1 (PD-L1) after chemotherapy in various tumors via MAPK activation and STAT1 inhibition to improve the efficacy of T cell-mediated immune killing in tumors, suggesting that chitosan oligosaccharide may be used to enhance the effectiveness of current chemotherapies [**86**]. Chitosan nanoparticles have been shown to enhance the radiosensitivity of

breast tumors in mouse models. Castro et al. demonstrated that combining chitosan/poly γ-glutamic acid nanoparticles (Ch/γ-PGA NPs) with radiotherapy induces antitumor immunity in the 4T1 orthotopic breast tumor mouse model [**9**]. Concomitant with glycated chitosan (GC), photodynamic therapy with Photofrin can improve the effects of inhibiting tumor growth, improving survival, enhancing local inflammatory reactions, and attracting acted immune cells to the tumor. It can also intuitively prove the systemic effect and long-term effect of laser immunotherapy (LIT) [**87**].

Chitosan may build up at the tumor site, starting the polarization of M1 macrophages and changing the immunosuppressive tumor milieu to an immune-supportive one, increasing the effectiveness of cancer immunotherapy and having an anticancer effect. In addition, chitosan has demonstrated potential as a drug carrier and therapeutic agent for its anticancer properties. Their ability to promote T-cell proliferation and hence start the production of cytokines is thought to be tied to their anticancer activity as a therapeutic agent. It has been noted that it blocks MMP-9 and strongly promotes apoptosis in tumor cells [**88**]. Dendritic cells (DCs) are activated by chitosan, which increases the anti-tumor activity of natural killer (NK) cells. Chitosan increased human NK cell IFN production when DCs were present. Chitosan worked by stimulating DCs to release pro-inflammatory cytokines like interleukin (IL)-12 and IL-15, which then stimulated NK cells' STAT4 and NF-B signaling pathways, respectively. Additionally, chitosan increased NK cell cytotoxicity against leukemia cells and supported NK cell survival [**89**].

The obstacles associated with passive drug targeting include the non-specificity of nanoparticles in locating target cells throughout the body, partly systemic side effects, and the cell membrane and cytoplasm of cancer cells that have several drug-capturing agents [**70**]. These obstacles can be avoided by employing drug targeting based on certain ligand-receptor methods and the physicochemical features of nanoparticles, which are termed "active drug targeting". The principal targeting moieties involve folic acid, polysaccharides, nucleic acids, peptides, and proteins because they have a high affinity for attaching to their receptors [**90**]. Folic acid is being investigated as a potential ligand for the folate receptor (FR), which would allow it to target the surface of cancer cells and effectively endocytose nanoparticles [**91**]. The glycosylphosphatidylinositol-anchored membrane glycoproteins FR-α and FR-β are overexpressed on the surface of a variety of human cancer cells, including those from the breast, ovary, liver, kidney, lung, and others. Due to the high affinities of FR-α and FR-β, this ligand is a suitable molecule for receptor-mediated internalization of CSNPs [**92**]. Nucleic acids are a potential ligand due to certain benefits such as biostability, a distinctive three-dimensional structure, and a low dissociation rate. These benefits open the door for high binding affinity, biocompatibility, non-immunogenicity, non-toxicity, easy preparation, and cost effectiveness [**93**]. Using CSNPs, certain receptors that are overexpressed on the surface of different cancer cells have been used for peptide and antibody-based

targeted delivery. For instance, integrins are a class of arginylglycylaspartic acid peptide (RGD) receptors that are abundantly expressed in a variety of cancers, including breast cancer. There are various types of RGDs, out of which cyclic peptides are more important for active drug targeting due to various characteristics such as tremendous binding discrimination, conformational stability, and low biodegradation [**94**]. A number of chemotherapeutic agents encapsulated in chitosan-based NPs have been summarized in **Table 2**. The drug targeting of cancer sites employing chitosan-based nanoparticles has been depicted in **Figure 5**.

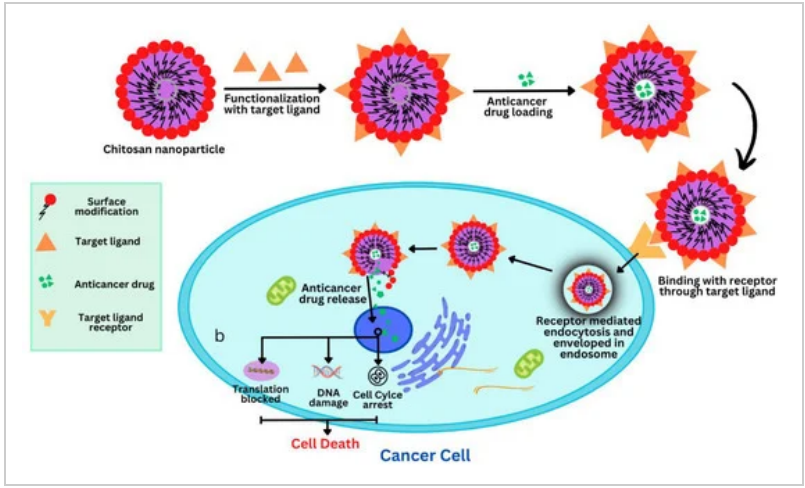



**Figure 5.** Representation of drug targeting to cancer cells employing chitosan-based nanoparticles.

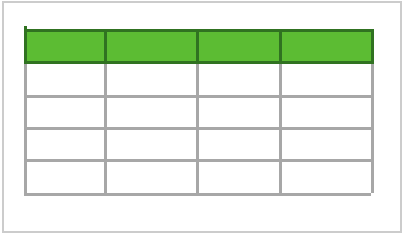
**Table 2.** A collective data of chitosan-based NPs encapsulating chemotherapeutic agents.

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Drug release from CSNPs depends mainly on two parameters: the composition of the drug product (drug, polymer, and excipients) and the method of fabrication. There are various mechanisms for drug release from the CSNPs, including diffusion-

controlled release, dissolution-controlled release, degradation- or erosion-controlled release, and stimuli-triggered release. In the current scenario, stimulus-triggered release is extensively employed for the controlled release of the drug at a specific site for the treatment of numerous kinds of ailments. In stimuli-triggered release, drug release can be initiated using internal or external stimuli at a specific site to enable the selectivity of a drug at this site. Internal stimuli include intracellular or extracellular alterations in pH, temperature, enzyme activity, ATP, and hormonal activities, while external stimuli include light, ultrasound, magnetic fields, mechanical stress, etc. This mechanism for drug release provides drug delivery at the desired site with minimal adverse effects. Various stimuli that trigger chitosan-based nanocarriers have been summarized in **Table 3**.

**Table 3.** A list of stimuli that trigger chitosan based nanocarriers for cancer treatment.

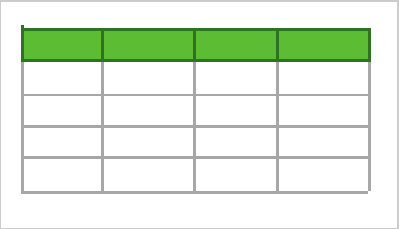


## 6. Chitosan Nanoparticles (CSNPs) for Codelivery of Drugs in Cancer Treatment

Codelivery of chemotherapeutic agents has emerged as a crucial strategy to overcome the challenges associated with the administration of conventional chemotherapeutic agents and phytochemicals in monotherapy, leading to increased therapeutic efficacy in cancer and decreased side effects [**133**]. Codelivery of drugs in cancer is advantageous because it possesses a variety of characteristics, such as fewer doses, which increase patient compliance, a decrease in multiple drug resistance, and fewer dosages, which lessen side effects in non-cancerous cells. Additionally, several studies have demonstrated the benefits of combining chemotherapeutic medications with phytochemicals, including a synergistic anticancer impact, the reversal of multiple drug resistances, and a reduction in side effects [**8**]. Various chemotherapeutic agents have been codelivered employing CSNPs, resulting in improved therapeutic efficacy. Li et al. developed chitosan nanoparticles for the codelivery of 5-fluorouracil and leucovorin in the treatment of colorectal cancer. It was observed that both drugs exhibited burst release initially, followed by continuous release at a later stage. The drug release was initially affected by their drug concentration, which indicates that drug release from nanoparticles could be controlled by altering the drug concentration at the initial point [**134**]. Jia

et al. fabricated mitomycin C and methotrexate-loaded PEGylated CSNPs for targeted drug delivery and synergistic effects. It was found that PEGylated CSNPs have nanometric size, constricted particle size, proper multiple drug loading, and sustained drug release. Based on in vitro cell viability testing, it was concluded that CSNPs showed concentration- and time-dependent cytotoxicity. Furthermore, it was observed that SCNPs could be taken effectively by cancer cells via folic acid receptor-mediated endocytosis [**135**]. In another study, Khan et al. fabricated CSNPs for the delivery of curcumin and cisplatin to treat ovarian cancer and observed that the optimized formulation exhibited a particle size of 225 nm and an encapsulation efficiency of 80%. The pattern of drug release displayed controlled drug release for both cisplatin and curcumin together and a lack of burst release. In addition, the cytotoxicity and uptake of both drugs in NPs showed augmented chemosensitization and increased therapeutic efficacy of both drugs [**136**]. Various chemotherapeutic agents codelivered employing chitosan nanoparticles have been summarized in **Table 4**.

**Table 4.** A collective database of Codelivered chemotherapeutic agents using chitosan-based NPs.



## 7. Surface Modification of Nanocarriers Using Chitosan

Despite the wide applicability of various nanocarriers in the treatment of cancer, these have some issues that lead to their poor therapeutic efficiency. Liposomes suffer from various issues such as drug leakage during prolonged storage, poor stability in aqueous media causing reduced shelf life, destabilization of liposomal membranes by pH, bile salts, the acidic pH of the gastric region, and elimination from systemic circulation on intravenous administration. These issues cause a reduction in the efficiency of liposomes in delivering therapeutic agents at the desired site in sufficient amounts [**145**]. Lipid-based nanoparticles, namely solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs), have poor stability in gastric pH on oral intake, poor encapsulation efficiency, poor stability, well-organized lipid structure, burst release of the drug, lack of drug targeting, and poor drug permeation, which cause obstacles in the therapeutic efficiency of drugs embedded in lipid

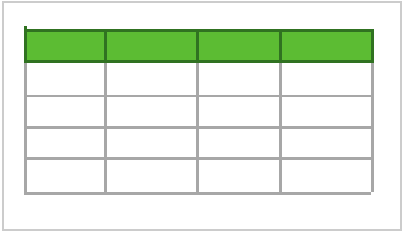
nanoparticles [**146**,**147**]. Nanoemulsions (NEs) also have stability issues that lead to creaming, Ostwald ripening, sedimentation, coalescence, and flocculation, enabling poor therapeutic efficacy of drugs loaded in NEs [**148**]. In addition, PLGA nanoparticles suffer from poor residence time on mucosal tissues, resulting in poor efficiency [**149**]. To overcome all these issues, surface modification is a promising way that has been extensively used to improve the therapeutic efficiency of nanocarriers in recent years. Surface modification of nanocarriers can be accompanied by various approaches, such as ligands, polymers, fatty acids, and surfactants. Polymer-based surface modification is widely used to improve penetration capability, controlled drug release, drug targeting to a specific site, and drug payload capacity [**50**]. Hasan et al. fabricated curcumin-loaded liposomes, followed by their coating with chitosan. It was found that the addition of a chitosan layer greatly boosted the liposomal dispersion stability by reducing the hysteresis loop area, as seen by the increase/decrease stress ramp. After the addition of chitosan, the viscoelastic characteristics studied by small-amplitude oscillatory shear rheology showed an improvement in mechanical stability. The liposome membrane structure was not impacted by the chitosan layer or the encapsulated curcumin, according to small-angle X-ray scattering tests [**150**].

In another study, NLCs having chloroaluminiumphthalocyanine were fabricated and functionalized using chitosan. It was observed that the encapsulation efficiency of functionalized NLCs was 96%, whereas it was only 79% for non-functionalized NLCs. Both formulations showed significant cutaneous retention of embedded agents after 2 h and 4 h of the investigation, respectively. The PDT in BF16-F10 melanoma caused cell viability to decrease by 50% and 70% for functionalized NLCs and non-functionalized NLCs, respectively [**151**]. Various anticancer drug-loaded nanocarriers functionalized using chitosan have been summarized in **Table 5**, and patents related to chitosan-based NPs to deliver chemotherapeutic agents have been summarized in **Table 6**.

**Table 5.** Summarized list of anticancer drug loaded nanocarriers functionalized using chitosan.

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**Table 6.** A list of patents for chitosan-based NPs for cancer treatment.





## 8. Conclusions

The prevalence and mortality of cancer have both been rising over the past few decades. Because of the sheer complexity of the disease, it has become extremely difficult, particularly concerning the quality of life of the patients. Recently, chemotherapy has been frequently used with surgery as a cancer treatment. However, chemotherapy has a low success rate as a treatment because of several issues, including side effects, drug resistance, the insensitivity of cancer cells to medications, a lack of targeting, and annoyance to the patient. Chitosan, a natural polycationic polymer derived from chitin, has advantageous properties such as biocompatibility, biodegradability, lack of toxicity, and mucoadhesiveness. It demonstrated promise in its application to cancer treatment through efficacious chemotherapeutic drug delivery. The presence of a reactive amino group on its backbone provides modified derivatives of chitosan with improved physiochemical and biological properties, which overcome the hurdle of poor aqueous solubility of chitosan. Chitosan and its modified derivatives can be employed to fabricate various drug delivery systems, including liposomes, nanoparticles, nanoemulsions, and metallic nanoparticles. CSNPs have emerged as interesting drug delivery systems for the delivery of chemotherapeutic agents in the treatment of cancer due to their possession of various advantages, including ease of manufacturing, biocompatibility, biodegradability, mucoadhesiveness, improved permeation, economics, and ecofriendliness. These nanoparticles can load both hydrophobic and hydrophilic drugs, shield the stability of drugs against various degradation mechanisms, and provide the release of drugs in a controlled and sustained manner at the target site. These have the potential to target the drugs using both active and passive mechanisms as well as stimuli responsiveness at cancer sites, which has centered the attention of researchers on using CSNPs for drug delivery in treating cancer. CSNPs have provided remarkable solutions to a variety of problems encountered while administering chemotherapeutic agents to the cancer site, and it is anticipated that they will continue to create new pathways for effective drug delivery for cancer treatment in the future. Moreover, despite huge progress in chitosan-based nanoparticles, a combination of chitosan with other biodegradable polymers to make novel drug carriers is unexplored, which can open the door for research in the future.

## Author Contributions

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

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## Institutional Review Board Statement

Not applicable.

## Data Availability Statement

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## Conflicts of Interest

The authors declare no conflict of interest.

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3D%20The%20limitations%20associated%20with%20the%20conventional%20treatment%20of%20cancer%20have%20necessitated%20the%20design%20and%20development%20of%20novel%20drug%20delivery%20systems%20based%20mainly%20on%20nanotechnology.%20These%20novel%20drug%20delivery%20systems%20include%20various%20kinds%20of%20%5B...%5D) (https://www.facebook.com/sharer.php?u=https://www.mdpi.com/2370296) (/toggle_desktop_layout_cookie)

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Virmani T, Kumar G, Sharma A, Pathak K, Akhtar MS, Afzal O, Altamimi ASA. Amelioration of Cancer Employing Chitosan, Its Derivatives, and Chitosan-Based Nanoparticles: Recent Updates. *Polymers*. 2023; 15(13):2928. https://doi.org/10.3390/polym15132928

### Chicago/Turabian Style

Virmani, Tarun, Girish Kumar, Ashwani Sharma, Kamla Pathak, Md Sayeed Akhtar, Obaid Afzal, and Abdulmalik S. A. Altamimi. 2023. "Amelioration of Cancer Employing Chitosan, Its Derivatives, and Chitosan-Based Nanoparticles: Recent Updates" *Polymers* 15, no. 13: 2928. https://doi.org/10.3390/polym15132928

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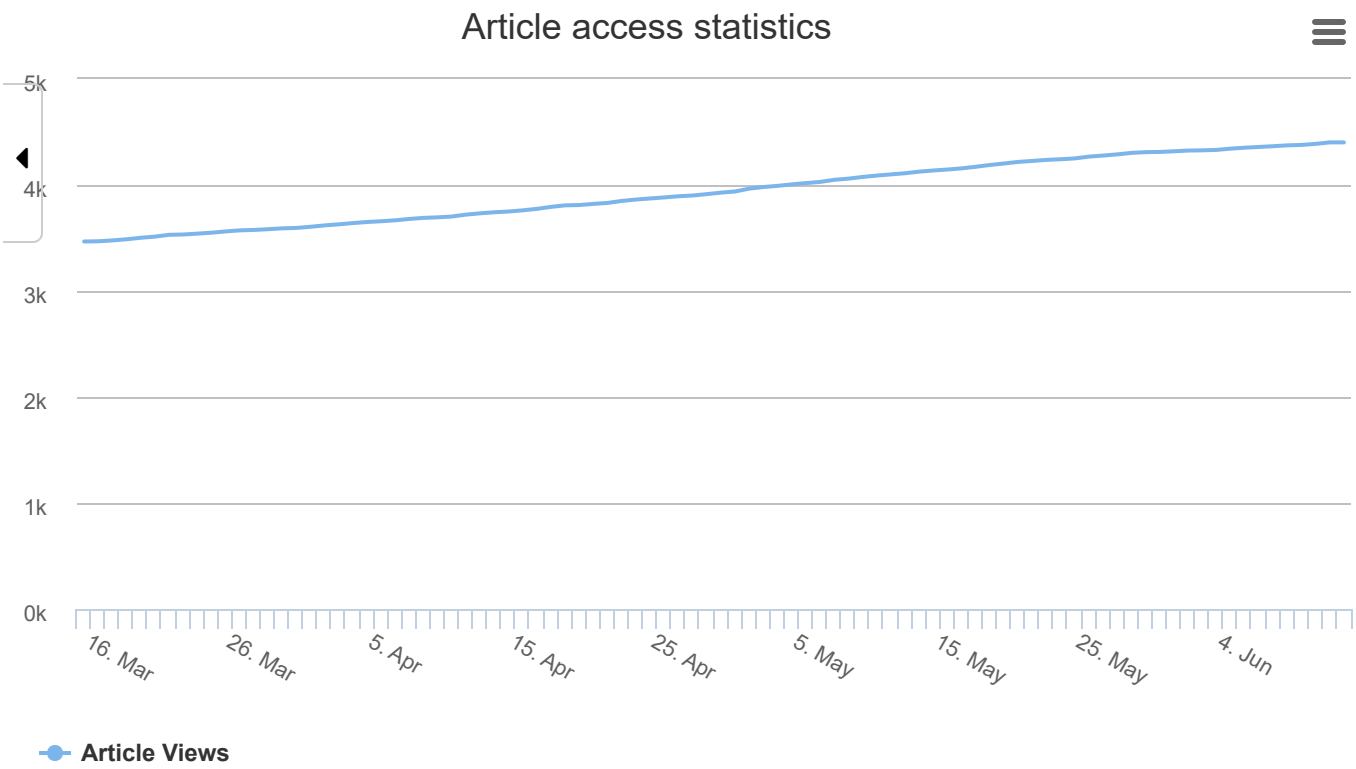
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# Functionalized and Nonfunctionalized Nanosystems for Mitochondrial Drug Delivery with Metallic Nanoparticles

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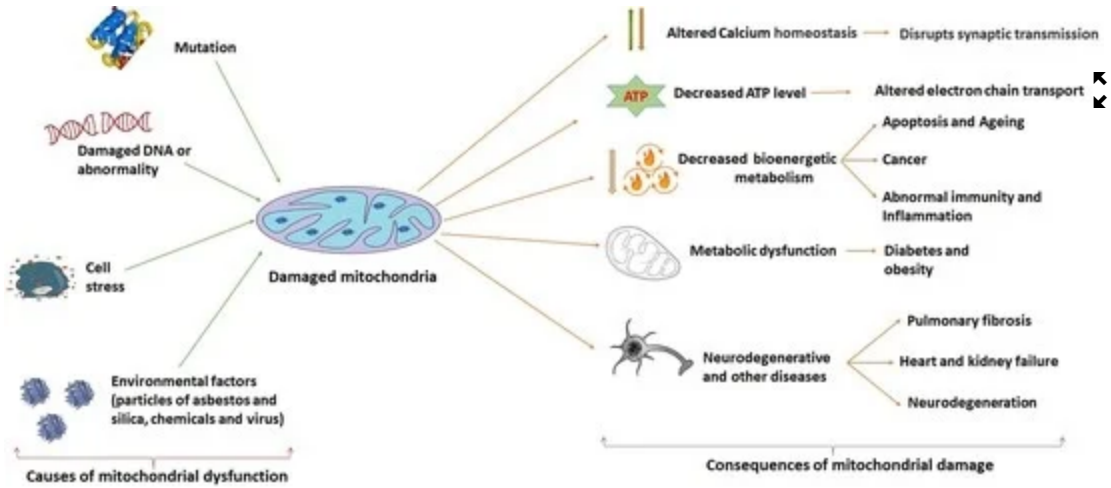
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## Abstract

**Background:** The application of metallic nanoparticles as a novel therapeutic tool has significant potential to facilitate the treatment and diagnosis of mitochondria-based disorders. Recently, subcellular mitochondria have been trialed to cure pathologies that depend on their dysfunction. Nanoparticles made from metals and their oxides (including gold, iron, silver, platinum, zinc oxide, and titanium dioxide) have unique modi operandi that can competently rectify mitochondrial disorders. **Materials:** This review presents insight into the recent research reports on exposure to a myriad of metallic nanoparticles that can alter the dynamic ultrastructure of mitochondria (via altering metabolic homeostasis), as well as pause ATP production, and trigger oxidative stress. The facts and figures have been compiled from more than a hundred PubMed, Web of Science, and Scopus indexed articles that describe the essential functions of mitochondria for the management of human diseases. **Result:** Nanoengineered metals and their oxide nanoparticles are targeted at the mitochondrial architecture that partakes in the management of a myriad of health issues, including different cancers. These nanosystems not only act as antioxidants but are also fabricated for the delivery of chemotherapeutic agents. However, the biocompatibility, safety, and efficacy of using metal nanoparticles is contested among researchers, which will be discussed further in this review.

**Keywords: metallic nanoparticles (/search?q=metallic+nanoparticles)**; **mitochondrial dysfunction (/search?q=mitochondrial+dysfunction)**; **antioxidants (/search?q=antioxidants)**; **reactive oxygen species (/search?q=reactive+oxygen+species)**; **calcium homeostasis (/search?q=calcium+homeostasis)**; **biocompatibility (/search?q=biocompatibility)**

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Graphical Abstract

## 1. Introduction

Mitochondria, one of the vital cell organelles, is notable as being oval or bean shaped, as well as for containing a dynamic branched system that consistently divides and fuses in accordance with the regulation of fission and fusion theory [**1**]. Mitochondria are the energy generator of eukaryotic cells, in addition to producing the adenosine triphosphate (ATP) that performs diverse functions, including the biosynthesis and degradation of protein molecules, cell division and respiration, as well as controlling membrane potential. They are adorned with countless cristae in the inner membrane of mitochondria, which are specifically involved in the generation of ATP on a massive scale. Besides the generation of ATP, mitochondria also perform numerous other tasks, such as the biogenesis of amino acids, ROS signaling, calcium ion homeostasis, apoptosis, stem cell monitoring, and the control of innate immunity [**2**]. Further, the bidirectional drive between the nucleus and ATP generator is tightly regulated via the fission (inner membrane) and fusion (outer membrane) of mitochondria. Diverse physical platforms (including signaling pathways, protein–protein interaction, and the regulation of both calcium homeostasis and released reactive oxygen species) occur in the powerhouse of the cell. A number of metabolic processes, such as glycolysis, the Krebs

cycle, oxidative phosphorylation, and acetyl CoA oxidation, are executed in the mitochondria, both for the purpose of ATP generation, as well as for dumping released electrons from the various pathways.

The mitochondria has an extremely flexible ultrastructure, intended for the regulation of the bioenergetics flux of the cell. The literature maintains that the sequence of mitochondrial genome (MtDNA) can stabilize maternally inherited diseases. Additionally, the proteomics of mitochondria has described approximately 1000 proteins inside the nuclear genome, of which a mere 13 proteins are coded by the mitochondrial DNA. Hence, quality control of mitochondria is critically important to avoid genome defects, as well as to maintain cell metabolic homeostasis [**3**]. The production, regulation, and consumption of organic molecules are highly required for supporting cell growth and proliferation. Mitochondrial oxygen utilization is key process that generates ATP from these organic compounds and other valuable intermediates. Besides ATP generation, reactive oxygen species (ROS) are also produced during the process of oxidative phosphorylation. These ROS mediate the signaling pathways associated with several basal and adaptive responses controlling both cell and organism hemostasis [**4**].

A myriad of mitochondrial targeted approaches were set up for targeting the mitochondrial proteins and signaling pathways concerned with the biogenesis and dynamics of mitochondria. The enhancement of antioxidant bioavailability via the supply of natural products is a fascinating strategy to address mitochondrial dysfunction. Nanoengineered novel drug delivery systems offer advanced tools and techniques for successfully delivering active drugs to the targeted site (mitochondria). In this context, several polymeric, vesicular, and metallic nanoparticles have been effectively developed for the alleviation of mitochondrial defects.

## 2. Mitochondrial Dysfunction and Diseases

Human cells comprise more than a thousand replicas of mitochondrial DNA (MtDNA). At the time of birth, these are homoplasmy that may be altered due to pathogens or mutation, and can consequently develop wild type MtDNA, or heteroplasm. The threshold of pathogenic MtDNA varies from person to person, and from organ to organ in the same individual. Abnormal mitochondria dynamics (i.e., fission and fusion), reduced oxidative phosphorylation capacity, and a transformed electron transport chain can each elicit ATP scarcity, alter ROS with poor membrane potential, and cause specific stress signaling responses. The resultant poor mitochondrial protein transportation influences enzyme assembly, which initiates several consequences, such as oxidative damage, proteotoxic stress, mutation, and the exhaustion of MtDNA. The altered morphology and functions of mitochondria can interrupt their nutrient requirements, substrate availability, and genetic signals,

causing inherited MtDNA mutations which thus weaken its defense system. **Figure 1** outlines the prominent features of the outer, inner, associated plasma membrane and cytosolic barriers.

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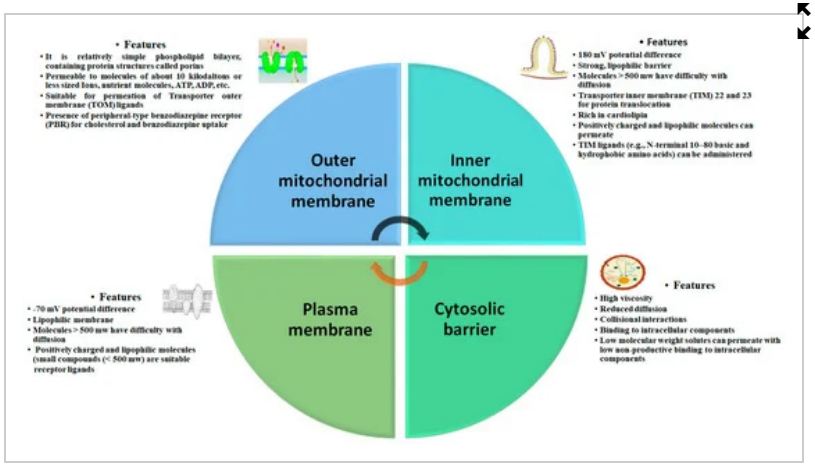



**Figure 1.** Interconnected distinguishing features and processes occurring in the mitochondria and associated sites.

Clinical studies have revealed that progressive aging is implicated with mitochondrial impairment, and that the release and accumulation of ROS plays a crucial role in pathogenesis of age-related issues, including neurodegenerative disorders and diabetes. The imbalanced level of generation and oxidation of ROS disturbs the respiratory chain function of mitochondria, altering not only outer/inner membrane permeability, but also calcium homeostasis and high heteroplasmic MtDNA in the sufferers [**5**]. Mitochondrial abnormality (either by MtDNA or nDNA) may occur at any age, and can affect single or multiple organs, e.g., the eye and ear. Both Leber hereditary optic neuropathy and nonsyndromic hearing loss (or deafness) have been reported as being due to abnormal mitochondrial functions. The literature reports noticeable clinical features, such as pigmentary retinopathy, cardiomyopathy, diabetes mellitus, and disorders in central nervous system (i.e., ataxia, dementia, seizures, fluctuating encephalopathy, and migraine), as being associated with the abnormal functioning of mitochondria. **Figure 2** illustrates primary and secondary mitochondrial disorders and their operational issues.

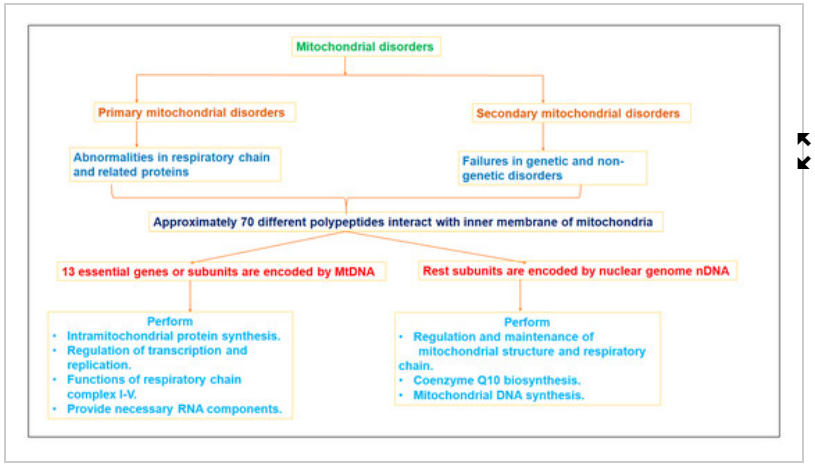





**Figure 2.** Mitochondrial disorders (primary and secondary) and their operational issues.

Recently, Friedreich's ataxia (a neurodegenerative defect) has been identified due to mitochondrial imbalance of ROS and reactive nitrogen species (RNS). One of the mitochondrial proteins, named frataxin, is encoded and arranged by the FXN gene, which is tremendously expressed in tissues with high metabolic rates. Frataxin is vitally involved in accumulation of the iron–sulfur clusters required for energy production. The latest evidence proposes that this protein deactivates the glutathione peroxidase enzyme, elevates thiol levels, and detoxifies the ROS associated with Friedreich's ataxia. Hence, targeting this protein may be a possible approach for a drug delivery system [**6**]. Genetic disorders such as Wilson's disease, hereditary spastic paraplegia, and ethylmalonic aciduria are caused by the mutation of ATP7b, SPG7, and ETHE1 genes, respectively [**7**]. **Table 1** compiles different diseases caused by damaged mitochondria, as well as the primary methods of their management.

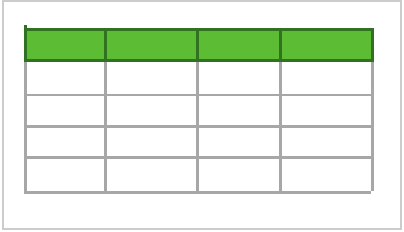
**Table 1.** Mitochondrial abnormalities and their management in different human diseases.

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## 3. Therapeutic Approaches

Approaches such as ‘one size fits all’ and ‘precision medicine’ are often employed for the mitigation of primary mitochondrial disorders. The former manages symptomatic interventions (based on diet, exercise, and pharmacological therapeutics) that initiate mitochondrial biogenesis, provoke nitric acid synthetase, amplify ATP synthesis, control mitochondrial autophagy, and stimulate fission/fusion processes. On the other hand, the precision medicine approach focuses on specialized therapies, i.e., nucleotide supplementation, swapping of damaged MtDNA, gene replacement remedies, the elimination of noxious metabolites, and organ transplantation, if required. **Table 2** compiles several therapeutic agents for the regulation of the myriad pathways involved in impaired mitochondria.

**Table 2.** Therapeutic agents explored for the management of impaired mitochondria.



These approaches may represent a common tactic for the management of primary mitochondrial disorders and can improve an individual’s quality of life, but they are unable to eradicate the cause of the mitochondrial disorder completely.

## 4. Biological Barrier and Toxicity

There are myriad barriers to designing mitochondria-targeted drug delivery, such as biological barriers and drug toxicity. After reaching to the target cell, intracellular diffusion across the outer and inner mitochondrial membrane is another challenge. Further, mitochondrial complex (I–IV) inhibition within ETC from drugs such as haloperidol and thiothixene have shown critical toxicities [**26**]. Resultantly, neurological disorder such as Parkinson’s disease arise. Nanotechnology-based approaches are promising tools for effectively targeting mitochondria, owing to their narrow size and their efficiency in transporting bioactive agents. Both the mitochondrial membranes experience variable permeability, i.e., the outer membrane allows the permeation of a large array of small molecules, whereas the inner membrane is quite selective for transportation. The reason behind selective

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permeability through the inner mitochondrial membrane is the presence of specialized channel proteins there [**27**]. Further, the transition pore of the outer mitochondrial membrane is wider than the inner mitochondrial membrane, which facilitates the faster traversal of therapeutics. The highly folded inner mitochondrial membrane is hard and possesses narrow transition slits to separate out the mitochondrial matrix within the inter membrane space. This characteristic morphology of mitochondria also poses a barrier for the passage of drug molecules across matrix. The aforesaid issues create hurdles for targeting mitochondria-based disorders. Several aspects, including high negative membrane potential (−160 to −180 mV), unambiguous protein import mechanism, variable lipophilicity, and idiosyncratic phospholipid composition of inner membrane, are a few key factors considered while designing a mitochondrion-targeted drug delivery system [**28**]. Permeation of the outer membrane of mitochondria is concentration dependent, following passive diffusion. A negative surface charge and mitochondrial membrane potentially drive the production of ATP, in addition to exploiting for mitochondrial targeting through cationic ions and drug molecules via electrostatic interaction. Cardiolipin, another exclusive phospholipid-based component, is confined and produced in the inner mitochondria region. It plays a central role in processing several reactions and processes required for mitochondrial dynamics and respiratory chain complexes [**29**]. Moreover, electrochemical composition and membrane potential are remarkably distinct, compared to cytoplasm. A mitochondrion comprises its own genome in form of a circular DNA containing 37 genes and 16,500 base pairs, essential for protein synthesis. The synthesized 13 proteins are basic components of the mitochondrial electron transport chain, as well as performing the process of oxidative phosphorylation [**30**]. Mitohormesis is related to the damaged adaptive response of mitochondria, and was very first discussed by Ristow et al. in 2010. This process controls mitochondrial homoeostasis and assists organismal senescence. The literature supports that increased age favors defects in mitochondria (mitophagy), replacing new mitochondria via the process of fission and biogenesis [**31**]. Therefore, the mitochondria’s basic functions deteriorate with aging, and can bring about several age-related disorders. In this context, drug-induced cell and mitochondrial toxicities are extensively demarcated in the geriatric population into myriad categories of pharmacological agents [**32**]. For example, troglitazone (an antidiabetic drug) exhibited mitochondrial toxicity and was withdrawn from the market after liver dysfunction was reported. The drug potently disrupted mitochondrial-oriented respiration by inhibiting complexes II, III, IV, and V [**33**]. Another, nefazodone (a serotonin antagonist) has been withdrawn from the market in United States in the year 2004 due to profoundly inhibiting mitochondrial respiratory chain in isolated rat liver cells [**34**]. Biguanides (buformin, metformin, and phenformin) trigger lactic acidosis, which is directly associated with mitochondrial damage due to a surge in lactate production and respiratory inhibition [**35**]. An over-the-counter drug, aspirin is the most prescribed medicine in elderly patients for overcoming of pain and has been reported to inhibit respiratory processes, as well as

opening MPT pores and disturbing of glutathione status in mitochondria [**36**]. Another cholesterol lowering drug, simvastatin, obstructs the ETC complexes I, IV, and V, augments calcium release, reduces mitochondrial membrane potential, and thus decreases ATP levels [**37**]. Further, both the in vivo administration of impoverished pharmacokinetic properties and the erratic biodistribution of drugs create challenges for the design of delivery systems. In many instances, therapeutic agents lost their potency with the addition of selective coding for the targeting of mitochondria.

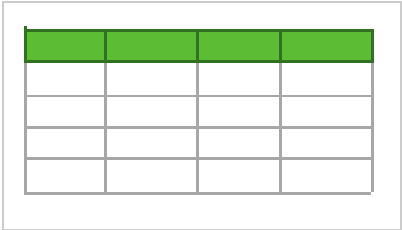
## 5. Nanoengineered Mitochondria Targeted Approaches

Nanotechnology is able to advance the pharmacokinetic and biodistribution profiles of various drug molecules without altering their pristine molecular form. The nanoformulation of drugs can modify the inherent physicochemical attributes of drugs, such as solubility, lipophilicity, half-life, and minimization of immunogenicity. Successful delivery of bioactive substances with the use of nanoparticles can be realized by customizing particle size, lipophilicity, surface charge, and the addition of specific targeting moieties. Being biocompatible and biodegradable, nanoparticles have proven potential for site-specific delivery [**38**], in addition to the intracellular targeting of subcellular compartments. It is evident that the architecture of mitochondria is highly distinct from other subcellular parts in eukaryotic cells. The occurrence of proton pumps in the inner mitochondrial membrane creates positive charges on the inner folded surface, whereas a negative charge is found in the mitochondrial matrix. This charge gradient develops noticeable transmembrane potential across both outer and inner mitochondrial membranes [**39**]. Molecules such as pyruvates and lipophilic cations (i.e., triphenylphosphonium, rhodamine123, and tetrachlorotetraethylimidacarbocyanine) have been reported on for targeting mitochondria. The cationic lipoidal content of these molecules enables their permeation into the mitochondrial matrix, thus effectively targeting the region of interest. Positively charged nanoparticles induce an electrostatic interaction with the anionic phospholipids of mitochondrial membranes, and are then internalized. Inside the membrane, the nanoparticles rupture and release their drug with the mitochondrial matrix [**40**].

Recently, the cationic liposome-like vesicles known as ‘DQAsomes’ have been highly researched as mitochondria-targeted carriers, being explored to deliver cytotoxic therapeutics or DNA into the highly negative environment of cancer cells [**41**], as these cells experience hyperpolarized membrane potential (−220 mV) compared to the mitochondrial membrane potential of normal cells (−140 mV). Bolalipids containing DQAsomes are vesicle-like structures that are tuned for the delivery of DNA, genes, and peptides inside the mitochondrial matrix. The entrapped component is selectively transported via adorned protein

pump machinery on the surface of mitochondria. DQAplexes are hybrid assemblies, comprising membrane liposomes with plasmid DNA for delivery of chemotherapeutics (specifically, into the mitochondria). Vaidya et al. conjugated folic acid on the surface of paclitaxel-entrapped DQAsomes to target overexpressive folate receptors on HeLa (tumor) cells. Outcomes obtained from confocal laser scanning microscopy revealed the enhanced antitumor activity of the designed functionalized DQAsomes, compared to bare DQAsomes [**42**]. However, the modi operandi for restricting the precise mitochondrial targeting of this system were unclear. Other nanoengineered dendrimers with high generation number are abundantly promoted to deliver cytotoxic agents to the mitochondria. Cations (such as triphenylphosphonium, polyamidoamine, and rhodamine) containing dendrimers encompass high net-positive charges and had the ability to carry genetic materials and chemotherapeutic agents at the cell organelle [**43**]. **Table 3** summarizes the various nanodrug delivery systems utilized for the management of damaged mitochondria-based diseases.

**Table 3.** Nanoengineered systems for mitigation of impaired mitochondrial diseases.



Metal-based nanoparticles of sizes ranging between 5 and 260 nm were suitable for entry into the mitochondrial matrix. Wang et al. synthesized gold nanorods, in addition to discussing the comparative cellular internalization and intracellular trafficking through the mitochondria, lysosomes, cytoplasm, and endosomes of both normal and cancerous cells. A seed-mediated growth method was utilized to design cetyltrimethylammonium–ammonium bromide wrapped gold nanorods. The average particle size and zeta potential of developed nanorods were 18 ± 0.5 nm and +29.3 ± 0.7 mV, respectively. The prolonged retention and cationic surface charge of the nanorods reduced the mitochondrial membrane potential and generated reactive oxygen species in the mitochondria of lung cancerous cells (A549 cells), which caused apoptosis or cell death [**51**]. **Figure 3** outlines the principal mechanism of metallic nanoparticles for targeting mitochondria.

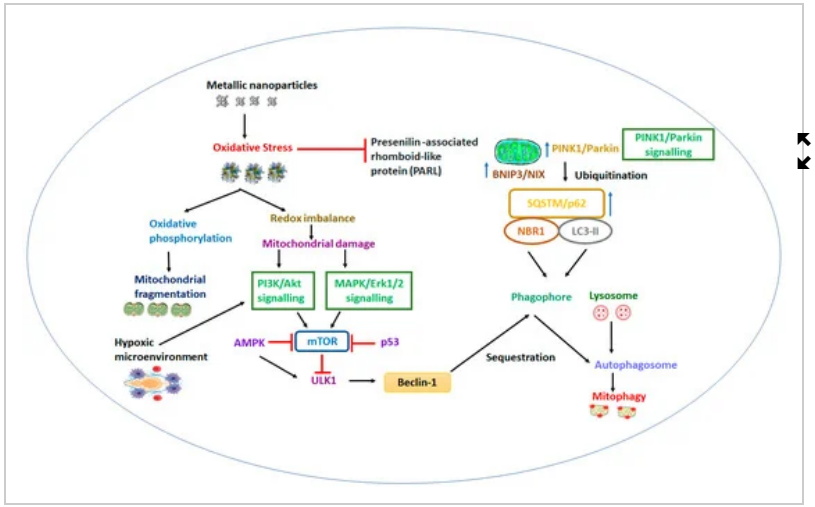



**Figure 3.** Schematic illustration on the mechanisms of metallic nanoparticles for targeting different pathway signals of mitochondria. PI3K: Phosphatidylinositol 3 Kinase; mTOR: Mammalian Target of Rapamycin; AMPK: Adenosine Monophosphate Activated Protein Kinase; Erk: Extracellular Signal-Regulated Kinase; Akt: Protein Kinase B; MAPK: Mitogen Activated Protein Kinase; ULK1: 112-kDa protein; BNIP3/NIX: Bcl-2 interacting protein 3; PINK1/Parkin-PTEN-induced kinase 1/autoinhibited E3-Ub ligase; SQSTM/P62: Sequestosome 1/p62 scaffold protein; NBR1: Ubiquitous Scaffold Protein; LC3-II: Ubiquitin-Binding Domain (Phosphatidylethanolamine conjugate).

However, the toxicity of metallic nanoparticles is reliant on biophysical characteristics, such as size, surface area, charge, and aggregation. These features affect biodistribution and internalization within organ systems, in addition to changing molecular interactions with receptors or macromolecules [**52**]. Published reports have suggested that there is a direct correlation between the particle size of nanoparticles and their efficiency to generate ROS in vital organs. For instance, silver nanoparticles with 10 nm size displayed superior biodistribution and caused more fatal effects in the liver and spleen cells, compared to the size range 40–100 nm [**53**]. As with the nanoparticle size, shape also affect biodistribution and clearance from the body. Long fibrous metallic nanoparticles exhibited more serious effects and were difficult to remove out from organ systems [**54**]. Similarly charged nanoparticles show greater accumulation in the target site compared to the noncharged ones. Peak et al. investigated the effects of particle size and surface charge of zinc oxide nanoparticles on pharmacokinetic parameters, including biodistribution and clearance upon administration of a single oral dose to rats. It was evident that

negatively charged zinc oxide nanoparticles were extensively absorbed by the systemic circulation, compared to those that were positively charged. Zinc oxide particles of 20 nm were swiftly eliminated through the biliary and fecal routes [**55**].

### *5.1. Gold Nanoparticles (AuNPs)*

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In recent years, studies on AuNPs in both the healthcare sector and pharmaceutical research have boomed. Both bioaccumulation and cytotoxicity of AuNPs inside the eukaryotic cells are fascinating researchers. Lopez-Chaves et al. determined tissue dissemination, subcellular spotting, and toxic effects exhibited by gold nanoparticles (mean size 10–60 nm) on HepG2 and HT-29 cell lines. Inductively coupled plasma mass spectrometry was utilized to estimate bioaccumulation of gold inside the essential organs (i.e., liver, kidney, intestine, and spleen). However, performing transmission electron microscopy revealed their subcellular location in colon cells. These AuNPs were quite active for the overproduction of reactive oxygen species and free radicals, initiating lipid peroxidation and protein carbonylation, in addition to the depletion of DNA. The lowest sized AuNP exhibited more deleterious effects in the mitochondria and nucleus. Their pronged retention lessens mitochondrial potential and augments reactive oxygen species level, which mediates apoptosis, and is required for the designing of organelle-targeted nanoplatforms for chemotherapy [**56**]. Salnikov et al. explored calibrated AuNPs to sense the outer mitochondrial membrane that serves as the last barrier between the cytoplasm and mitochondria. The particle size was monitored, and the results suggested that, under normal (control) conditions, the outer mitochondrial membrane of the rats' permeabilized ventricular cells was impermeable to 6 nm sized gold nanoparticles. That said, a 3 nm particle size was capable of entering the intermembrane space of mitochondria of isolated cardiac tissue 20 times more efficiently than the permeabilized ventricular cells. Further, voltage-dependent anion channel, 4,4′–di-isothiocyanatostilbene-2,2-disulfonic acid, and Konig polyanion tend to inhibit the entrance. Results gathered from green fluorescent protein concluded that the low availability of voltage-dependent anion channel (VDAC) within the outer mitochondrial membrane of cardiac mitochondria comprised a pore diameter >3 nm but <6 nm [**57**]. Gallud et al. studied responses of functionalized AuNPs on human monocytic cells. Both transcriptomics and proteomics concepts were included to demonstrate the cytotoxic effects of alkyl ammonium bromide, polyethylene glycol, and alkyl sodium carboxylate surface supplemented AuNPs. The results outlined a pronounced cytotoxic action and mitochondrial-dependent effects from the cationic ammonium terminated AuNPs, revealing an aggravated autophagy in RFP-GFP-LC3 receptor cells. However, no significant cell death was noticed in human leukemia monocytic cells (THP-1 cells) through PEGylated and carboxylated AuNPs [**58**]. Chen et al. developed a nanocomposite containing a gold nanostar and doxorubicin (anticancer drug). Hyaluronic acid is coencapsulated to protect the shell and enhance both the

phototherapy and chemotherapy action. This nanosystem was modified, with proapoptotic peptide being added via sulfur bond. The nanocomposites were regular, with an average mean size of 40 nm. The decorated cationic peptide R8 and mitochondrial targeted triphenyl-phosphonium-KLA peptide did not disturb either the anatomy or the morphology of mitochondria. It was also observed that synthesized nanoplatform (i.e., AuNS-pep/DOX@HA) was successfully internalized into the cancerous cells via mediation of cell surface adhesion receptors (CD44). Further, coated hyaluronic acid was digested by the hyaluronidase enzyme, facilitating the release of doxorubicin in the subcellular site (mitochondria) after near-infrared light triggering photothermal therapy in vivo [**59**].

### *5.2. Iron Oxide Nanoparticles*

To safely and effectively target mitochondria, a mitoNano approach encompassing different nanoparticles displays a potent role in the advanced management of cancer. This approach overcomes issues such as drug resistance and side effects. Classical multifunctional chemotherapeutic-embedded metallic nanoparticles are modified and functionalized to tailor their biocompatibility, as well as being potentiated with the effect of light. This photothermic or photodynamic property facilitates the selective delivery of metallic nanoplatforms into the mitochondrial cells [**60**].

Iron oxide nanoparticles are a widely explored nanoplatform, owing to their exclusive superparamagnetic properties. Despite being biocompatible, they have excellent ROS productive capacity, due to their ability to cause Haber–Weiss reactions. Produced highly reactive hydroperoxy radicals trigger oxidative stress and disrupt the DNA that mediate mitochondrial malfunction. Interestingly, iron oxide nanoparticles have the potential to behave like enzymes and catalyze reactions in presence of hydrogen peroxide and acidic solution, resulting in the production of highly toxic hydroxyl radicals that can be applied in cancer management [**61**]. Khan et al. synthesized iron oxide nanoparticles (size range 30–65 nm) using the sol–gel method to induce autophagy selectively in the A549 cancerous cells. Autophagy is a catabolic process that follows from the breakdown of carbohydrates, proteins, and lipids. It is exclusively related to the protein degradation system where cell protein contents and subcellular components are assimilated by lysosomal hydrolases, with the resultant production of ROS and mitochondrial abnormalities. In normal cells, autophagy maintains homeostasis via expelling out superfluous proteins and removing damaged or injured mitochondria, but it is highly important in the arena of chemotherapy research. Iron oxide nanoparticles have recently been acknowledged to induce autophagy by virtue of their cytotoxic action in mesenchymal stem cells, HeLa cells, A549, and fibroblasts of isolated lung tissue (IMR-90 cells) [**62**].

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Zhang et al. investigated comparative autophagy effect using magnetic iron oxide and its PLGA-coated nanoparticles. All nanoparticles (i.e., iron oxide, PLGA-coated iron oxide, and PLGA nanoparticles) were successfully internalized via a cellular endocytosis process. In the same manner as magnetic iron oxide nanoparticles, comprehensively impaired lysosomes caused mitochondrial damage and cell organelle stress which mediated LC-3 positive autophagosomes, whereas PLGA-coated iron oxide nanoparticles exhibited marginal effects on these organelles (Golgi body and endoplasmic reticulum). Further, the cytotoxic study in mice revealed greater autophagosome accumulation of magnetic iron oxide nanoparticles in the kidney and spleen, compared to PLGA-coated iron oxide and bare PLGA nanoparticles [**63**]. Rivas-García et al. targeted mitochondrial DNA through synthesizing iron nanoparticles measuring 2–4 nm in size. The effect on both mitochondrial function and the process of autophagy were monitored in colorectal cell lines (i.e., HT-29). Iron nanoparticles were capable of entering subcellularly (mitochondria), which affected both respiratory and glycolytic activities. Autophagy caused by iron particles was analyzed through fluorescence signal determination. Two different dyes (such as Hoechst33342 and Cyto-ID® Green dye) were employed, working as a subcellular permeation indicator and a green, fluorescent reagent in the treated cells (HT-29), respectively. Cells containing iron nanoparticles exhibited pre-eminently high autophagic vacuoles and intense fluorescence compared to the control. Further, iron nanoparticles were 62-fold more internalized in mitochondrial regions. Transmission electron microscopy revealed autolysosomes after 2 days (48 h) and concluded that exposure to small iron particles reduced number of MtDNA in colorectal tumor cells [**64**]. Ferroptosis therapy is concerned with cell death due to the deposition of iron-dependent lipid hydroperoxides. This new therapy has found application in the management of epithelial cell carcinoma. A nanodevice specific to the epithelial-to-mesenchymal transition has been designed, that worked on lipid peroxidase burst. The nanosystem was assembled on a mitochondrial membrane that had been magnetically sensitized. Sorafenib loaded in the self-assembly of supramagnetic iron oxide nanoparticles enhanced membrane permeability. The developed system released ferrous and ferric ions in the acidic environment of lysosomes that led to the bursting of the lipid known as hydroperoxidase. Approximately 18-fold higher accumulation was observed in the treated group of breast cancer cells. This ferroptosis therapy proved to be an alternate strategy for managing resilient epithelial cell carcinoma [**65**].

### *5.3. Silver Nanoparticles*

Silver nanoparticles (AgNPs) have found extensive application in pharmaceutical sciences owing to their superb antibacterial and cytotoxic activities. AgNPs display exceptionally superior physicochemical properties, making them a highly fascinating and demanding metallic particle in the sectors of biomedical research and healthcare. Their pre-eminent

antimicrobial activity is well established, while the development of a myriad of drug delivery systems is being explored. Nevertheless, the reported cytotoxic effects have elicited public concern with regard to their use in cosmetics and other household products. The literature contends that uptake and cell internalization of silver nanoparticles are via a clathrin-mediated process (a kind of endocytosis) within both lung fibroblasts and glioblastoma cells. Scanning electron microscopy revealed the uniform distribution of silver nanoparticles in the cell organelles. In nuclei, it causes a mitotic arrest that results in chromosome instability. Additionally, in mitochondria, AgNPs upset calcium transients through the activation of catabolic enzymes. In cancerous cells, silver nanoparticles inhibit cell proliferation by disturbing the signaling cascade pathway [**66**]. Recent research has focused on the wide application of silver nanoparticles to managing multidrug resistance in chemotherapy.

A study of the size-dependent cellular functions of silver nanoparticles (5 nm and 75 nm) was conducted by Gopisetty et al. in 2019, concluding that a particle size 75 nm had the potential to significantly inhibit the p-gp transporter efflux, disrupt mitochondria, create endoplasmic reticulum stress, and suitably manage drug-resistant breast cancer. The same effect was not observed in silver nanoparticles of 5 nm. However, both sizes of nanoparticles were quite sufficient to produce ROS and mitochondrial impairment [**67**]. Hou et al. have elaborated role of autophagy in the AgNP-induced cytotoxicity in the breast epithelium cells (HC11) of mice. HC11 cells released lactate dehydrogenase, which is predominantly associated with oxidative stress due to the augmented expression of hemoxygenase-1 and the liberation of both the reactive oxygen species (ROS) and nuclear factor erythroid 2–related factor 2 (Nirf-2). Further, mitochondrial membrane potential was found to be drastically reduced, whereas the level of parkin protein surged. Resultantly, the PTEN induced putative kinase (PINK 1) both activated and depolarized the mitochondria that lead to autophagy. Moreover, the administered silver nanoparticles influenced heterotrimeric AMP-activated protein kinase, which acts as sensor of cellular energy in mammalian adipose tissue. The protective autophagy in mitochondria lessened the expression of p-mTOR and p-Akt in HC11 mammary cells. The results suggested that silver nanoparticles can deteriorate mammary cells in clinical applications, which would impact lactation functions; it is hence suggested to be used with caution [**68**].

Another study on the effect of AgNPs on the mitochondrial redox mechanism was carried out in a panel of myriad lung cell lines, such as Calu-1, A549, NCI-H358, and BEAS-2B. AgNPs instigated the cell cycle, reducing proliferation of the cells of Calu-1, A549, and BEAS-2B. NCI-H358 cell lines were shown to be resistant against the action of AgNPs. Both the mitochondrial ROS and protein oxidation were enhanced upon being treated with AgNPs in a time- and dose-dependent manner [**69**]. Robust evidence supporting mammalian cells toxicity with the use of AgNPs has been reported in several literature reports and research. AgNPs are extremely associated with the generation of excessive ROS and a lowered level of

ATP by upsetting cellular oxidant and antioxidant stages. Consequently, mitochondrial dynamics are disturbed, which involves mitochondrial fission, autophagy, apoptosis, and further cell death. The mitochondrial outer membrane proteins comprise fission proteins (i.e., mitofusin 1, mitofusin 2, and mitochondrial fission factor), whereas the inner membrane of mitochondria contains fusion protein (optic atrophy 1). Fission proteins mediate mitochondrial fission by employing GTPase dynamic related protein 1. Li et al. studied exposure of AgNPs in human nontumorigenic cells (HepG2 cells), which resulted in the alteration of mitochondrial morphology and biogenesis. AgNPs were treated with polyvinylpyrrolidone and had an average mean size of 23.44 nm, with a uniform shape. In Dulbecco's Modified Eagle media, the particles exhibited improved size (51.58 nm) due to hydration. A cell viability study outlined a significant reduction in HepG2 cells in a time- and concentration-dependent manner, i.e., 20–640 µg/mL of silver nanoparticles for 24–48 h. The half inhibitory concentrations (IC50) of the designed silver nanoparticles in HepG2 cells after 24 h and 48 h were 1317.26 µg/mL and 301.6 µg/mL, respectively [**70**].

Though metallic nanoparticles are proven strategies for the deregulation of mitochondrial anatomy and functions, nanoparticles with antioxidant properties may induce mitophagy owing to their ability to alter both the signaling pathways (P13K/Akt/mTOR and Perkin pathway) and the levels of reactive oxygen species. Their optical, thermal, and physicochemical features have been explored, to combat various cancers and other critical ailments. Their enormous surface area and the presence of uncoordinated sites on their surface allows them to bind with therapeutics and bioactive agents, and thus perform catalytic action, facilitating precise delivery at the target site [**71**]. Their subcellular penetration efficacy (specifically towards mitochondria) makes metallic nanoparticles sensational in the biomedical research arena. The membrane potential difference and inhibition of mitochondrial respiration are major issues that can create apoptosis, mitophagy, and induce cell death in cancerous cells [**72**]. The mitochondrial dysfunction leads to cancer progression that involves several processes, including interrupted oxidative phosphorylation, reduced energy, reactive oxygen species accumulation, and inflammation in the cells. Therefore, mitochondria targeting is the emerging strategy to manage chemotherapy. Metallic nanoparticles, such as silver and zinc oxide, perform as an autophagy modulator and create a more stimulating signaling cascade in the tumor cells compared to normal cells [**73**].

Skalska et al. investigated pathological alterations, such as cristolysis and swelling in mitochondria, that presented in rat brains after exposure to AgNPs at 0.2 mg/kg concentration. Further, an augmented expression of beclin-1 and MAP LC3-II (protein markers) were observed to induce autophagy [**74**]. Several mitophagy adaptors, such as a parkin, PINK1, bifunctional mitochondrial protein (BNIP3), autophagic indicator (P62/SQSTM1) and signaling pathways (nuclear factor (erythroid-derived 2)-like 2 (Nrf2)/PINK1/Parkin pathway), are impaired in cancer [**75**]. Piao et al. proposed the crucial role of silver nitrate

nanoparticles in the suppression of glutathione level in the Chang liver cells of humans. Apart from ROS generation, both lipid membrane peroxidation and DNA fragmentation were also observed upon exposure to AgNPs. Thereafter, mitochondria dependent apoptosis (via the disturbance of mitochondrial membrane potential), the release of cytochrome C, the activation of caspases 9 and 3, and the variation on Bax/Bcl-2 expression were evident [**76**]. The potential application of AgNPs against human hepatoma (HepG2 cells) is also reported. Primarily, it induced mitochondrial swelling and enhanced intracellular level of ROS, which caused a collapse in membrane potential and mediated apoptosis via mitochondrial pathway. AgNPs concomitantly increased the autophagy marker proteins, such as LC3B and p62, that activate cytotoxicity in tumorous cells. **Figure 4** explains the numerous signaling pathways and their functions involved in the process of mitophagy.

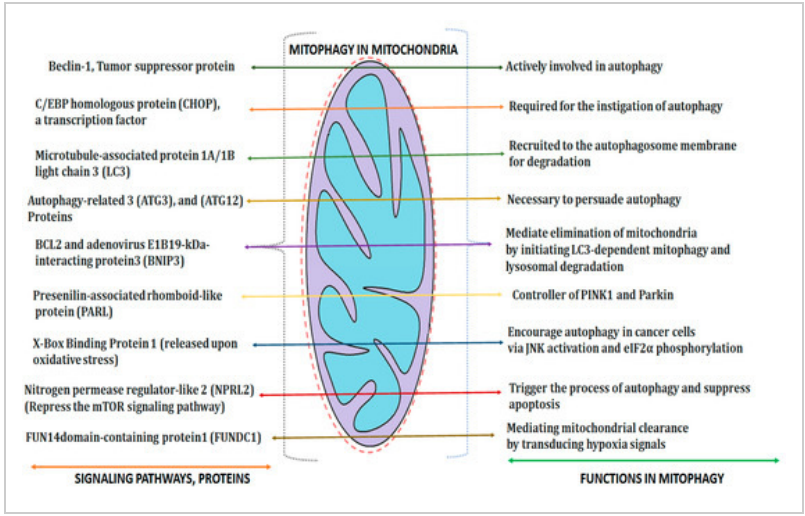
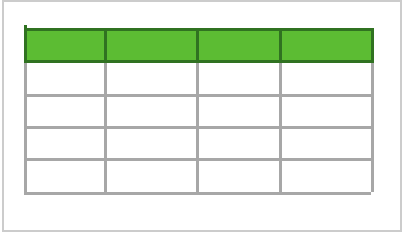



**Figure 4.** Various signaling pathways and their respective roles for ensuing mitophagy.

Breast cancer has garnered much interest among researchers. Although numerous therapies and treatments based on AgNPs are clinically approved, none of them completely cured the disease, nor proved to be a game changer. AgNPs are aggressively explored for their antitumor effect on the MCF-7 cell line. A study reported that AgNPs with a size of 9 nm successfully localized within the mitochondria and endoplasmic reticulum. This changed the mitochondrial dynamicity, depolarized membrane potential, generated ROS, and destabilized homeostasis. Resultantly, mitochondrial fission was initiated in breast cancerous cells. A study of their cytotoxicity revealed the apoptosis of MCF-7 via controlling the dynamicity of

mitochondrial-ER [**77**]. **Table 4** summarizes conjugated metallic nanoparticles and their mechanisms for targeting the mitochondria of cancer cells.

**Table 4.** Functionalized metallic nanoparticles explored for the management of cancer via targeting mitochondria.



### *5.4. Titanium Dioxide ($TiO_2$) Nanoparticles*

$TiO_2$ nanoparticles are extensively employed in different sectors, including food additives, cosmeceuticals, and environmental decontamination. However, the excessive and irrational usage of titanium dioxide creates serious health issues, including epigenetic changes in lung fibroblasts, hippocampal synaptic plasticity, and impaired placentation [**97**]. Nanoparticles of titanium dioxide were first explored in the year of 1990 for tissue engineering and drug delivery system applications. Recently, a lot of modifications have been brought $TiO_2$ to lessen the risk of its tumorigenic property. In this series, mitochondrial dysfunction (due to excessive oxidative stress) is also determined with $TiO_2$. The literature supports the understanding that imbalanced fission and fusion with the exposure of $TiO_2$ results in both structural and functional disturbances in mitochondria [**98**].

Yu et al. demonstrated the toxicological outcomes of $TiO_2$ nanoparticles (250 nm) in human bronchial epithelial cells that had been treated with a concentration range of 50–100 µg/mL for the period of 48 hrs. These nanoparticles trigger ROS generation and imbalance oxidative homeostasis inside the cells. The obtained results accurately described the destruction of mitochondrial-based endoplasmic reticulum membrane potential, as well as the disturbance of $Ca^{2+}$ dynamics and the induction of endoplasmic reticulum stress inside the cell, mediating autophagy. This disturbed cellular homeostasis led to protein misleading, and eventually to the apoptosis or even the cell death of bronchial cells. Contrary to this, treatment of human bronchial epithelial cells with an ER stress inhibitor (Tauroursodeoxycholic acid) alleviated the toxic responses caused by $TiO_2$ nanoparticles. This study recommends the performance of an exhaustive investigation on the harmful effects caused by $TiO_2$ nanoparticles on the mitochondria, to ensure its safe and effective application [**99**].

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Exposure of the skin to titanium dioxide is harmful in a daily routine and requires attention for the researchers when designing newer formulations. The various exposure pathways of $TiO_2$ (including inhalation and ingestion) may create serious issues to human skin. Brassolatti et al. evaluated the cytotoxic action of functionalized $TiO_2$ nanoparticles on human fibroblast (HDFn) and keratinocyte cells (HaCaT). The developed system contained a sodium carboxy ligand being added to the surface of $TiO_2$ nanoparticles. An MTT assay was performed to investigate mitochondrial activity in both the cells, revealing that at elevated concentrations (>100 µg/mL) severe destruction of cell membrane occurred, due to generation of ROS within 72 h. The results suggested that a concentration below than 10 µg/mL was safe, and no cell alteration was reported [**100**]. To investigate the efficiency of $TiO_2$ nanoparticles across brain cells, an exhaustive study was carried out by Huerta-García et al. in human and rat glial cells U373 and C6, respectively. Titanium dioxide nanoparticles disturb the redox signaling process and the peroxidation of lipids. High oxidation stress in both glial cells exhibited surged levels of oxidative enzymes, including glutathione peroxidase, superoxide dismutase, and catalase, which resulted in morphological changes, such as damage in mitochondria, and high membrane potential. The results revealed that $TiO_2$ may enter into the brain cells via the olfactory bulb, where they are deposited in the hippocampus site, and hence exhibit cytotoxic action [**101**].

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Zhao et al. investigated the alterations of mitochondrial dynamics due to exposure to $TiO_2$ nanoparticles in the hippocampal neuronal cell line (HT22 cells). The results obtained through both the stimulated emission depletion and confocal microscopy demonstrated noticeable changes in mitochondrial length/density (submitochondrial structure) upon treatment with $TiO_2$ nanoparticles. The nanoparticle causes a dynamic imbalance in the expression of optic atrophy 1 and dynamic related protein 1. Thereafter, $TiO_2$ nanoparticles stimulate mitochondrial-based apoptosis via changing the signal pathways, including Bax, Bcl-2, and caspase 9 in the selected HT22 cells [**102**]. In the inner membrane of mitochondria, a special phospholipid called ‘cardiolipin’ is found that critically regulates the electron transport chain. $TiO_2$ nanoparticles (10 nm) downregulate the cardiolipin profile and cause dysfunction in ATP production. Consistently, exposure to these nanoparticles significantly augmented dose-dependent ROS accumulation in mitochondria of bone-marrow-derived macrophages. Chen Q et al. quantified metabolic flux using a tracer (carbon 13 labelled glutamine) in a TCA cycle. The results described the dose-dependent decrement in the TCA metabolites, which was also supported by the reduced level of cardiolipin [**103**]. A thorough study on the molecular mechanisms and effect of $TiO_2$ indicated that (around the tumor) microenvironmental influences are revealed, including metabolic changes, protein degradation, and gene mutation [**104**].

### *5.5. Zinc Oxide (ZnO) Nanoparticles*

ZnO nanoparticles are widely employed in a diverse range of industrial sectors, including food additives, electronics, cosmetics, sunscreen products, and drug delivery approaches. These particles also possess anticancer and antimicrobial properties, owing to their efficient absorbance of ultraviolet and transparent visible light [**105**]. The wide applications of consumable products containing zinc oxide create alarming health issues. Sharma et al. demonstrated prominent adverse effects on liver, a primary site of metabolism in living beings. Both the genotoxic and apoptotic potential of zinc oxide was observed in HepG2 liver cells at a concentration of 14–20 µg/mL for 12 h. Significant decrement in cancer cell viability, due to induction of oxidative stress and DNA damage, was reported. Released reactive oxygen species lessened the mitochondria's membrane potential via a surge in the Bax/Bcl2 signaling pathways. Further, the activation of p38, p53, and oxidative phosphorylation were also reported [**106**]. Nevertheless, the ion shedding property of ZnO nanoparticles categorized it as one of the most toxic and hazardous metal oxides compared to others (iron oxide, titanium dioxide, and aluminum oxide). Clinical studies performed in different eukaryotes and prokaryotes revealed prominent cell toxicity. ZnO nanoparticles are efficient for targeting and transporting anticancerous therapeutics (such as methotrexate) in the vital organs, such as the liver, lungs, and heart. The growing evidence of systemic inflammation and cardiovascular toxicity was predicted in the literature, due to permeation potential of ZnO across biological barriers. Oral exposure of ZnO nanoparticles disrupts DNA and elevates levels of both creatine kinase and troponin in rat hearts, whereas inhalation and intrathecal instillation create fibrosis, inflammation, and necrosis in rat myocardium [**107**,**108**]. Liang et al. have designed ZnO nanoparticles and investigated the associated cytotoxicity in human aortic endothelial cells. A dose- and time-dependent intracellular oxidative stress and cell membrane leakage were achieved at the concentration of 8–50 µg/mL after a day, in human aortic endothelial cells. Cytotoxicity was observed with undissolved $Zn^{(2+)}$ions, which induced apoptosis and necrosis after 24 h due to generation of ROS, which likewise impaired negative membrane potential, followed by the release of Cytochrome C, triggering caspase 3 and 9, and surging the ratio of Bax/Bcl-2 [**109**]. Exposure of ZnO against different cell lines, such as breast cancer and liver cancer MCF-2 and HepG2 cells, respectively, were investigated by Wahab et al. A nonprotonated chemical route was employed for the development of nanoparticles of size 13 ± 2 nm. The MTT assay revealed dose-dependent (2.5–100 µg/mL) cytotoxic activity and significant antiproliferation actions (95% and 96%; $p < 0.05$) against both HepG2 and MCF-7 cell lines. Fluorescence activated cell sorting (FACS) described a reduction in cell viability, whereas a real-time polymerase chain reaction demonstrated a substantial upregulation level of Bax, caspase 3, and p53, and a downregulation of Bcl-2, an antiapoptotic gene [**110**]. Bai et al. developed crystalline ZnO nanoparticles (20 nm) for the investigation of cytotoxicity and cell death (autophagy) in ovarian cancer.

A series of cellular assay/tools were engaged to define the mechanism behind the mitochondrial damage and apoptosis. A dose-dependent damaged cell viability (due to the disturbance of mitochondria's membrane potential and the generation of ROS or oxidative stress caused by the ZnO nanoparticles) were observed in treated ovarian cancerous cells. Damaged DNA strands were evident from the overexpression of γ-$H_2AX$ and Rad51 numbers. The Western blot analysis revealed the upregulation of p53, Bax, LC3, and caspase 9 with exposure of zinc oxide nanoparticles, which indicated the process of mitophagy and autophagy [**111**]. Zinc is also a common constituent of metal–organic framework (MOF) structures assembled from metal ions and polydentate ligands [**112**], and has recently been utilized in a new encapsulation technology that can deliver bioactive mitochondria inside cells. This novel technology is envisioned to be used for mitochondria, opening up a completely new avenue for the management of diverse mitochondrial diseases [**113**].

### *5.6. Selenium Nanoparticles*

One of the rarer metalloids, selenium (allied of sulfur and tellurium) has also been explored for the cancer prevention by virtue of its ability to induce ROS-mediated apoptosis in malignant cells. Moreover, it causes an antioxidation process in healthy cells, in very low doses. These properties attract researchers to its use in targeting mitochondrial cells for the improvement of anticancerous efficiency. However, tissue toxicity is always a matter of concern when designing mitochondrial-targeted strategies with selenium nanoparticles [**114**].

Recently, the usage of selenium nanoparticles has been reported in the neurological abnormalities where neurons are destroyed by oxidative stress. The literature supports the understanding that functionalized and nonfunctionalized selenium nanoparticles proved a better alternative for managing oxidative stress [**115**,**116**]. Varlamova et al. have developed a nanocomplex (100 nm) using selenium nanoparticles and taxifolin (a naturally occurring antioxidant) for the regulation of mitochondrial calcium dynamics. Taxifolin is a recognized natural remedy for ischemic pathologies, owing to its potential neuroprotective effect. Its compromised pharmacokinetic parameters (poor solubility, low permeability across BBB, and toxicity) limit its frequent use in the design of targeted formulations. The authors developed different nanoparticles containing bare taxifolin (TAX), selenium (Se), as well as with their amalgamation (nanocomplexes of SE–TAX), before evaluating them for their possible efficiency with respect to the suppression of ROS generation in the astrocytes and neurons that had been exposed to hydrogen peroxide exogenously. Results confirmed the comparatively high efficiency of the prepared nanocomplexes SE–TAX in significantly reduced concentrations, by the virtue of selenium, which activated antioxidant enzymes and restrained the ROS production system. It was also revealed that the developed nanocomplex inhibited the rise of calcium ($Ca^{2+}$) in cytosol, and

that oxygen–glucose deprivation (OGD) provoked hyperexcitation in the neurological system. Hence, the system exhibited potential efficacy for the regulation of $Ca^{2+}$ dynamics in the cell organelle, in addition to antiapoptotic effects and antioxidative properties [**117**,**118**].

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Another vital application of selenium conjugated with Lentinan was reported by Lie et al. Lentinan, a kind of β-glucan, is isolated from *Lentinus edode* and enriched with variety of pharmacological activities, before being employed for the management of malignant ascites. Lentinan-functionalized selenium nanoparticles were synthesized; they were biocompatible and exhibited apoptosis-inducing effects for combatting cancerous ascites. The modi operandi behind necroptosis were observed as comprising the degradation of lysosomes and mitochondrial dysfunction via targeting (TRAF3)/mitofusin (MFN1) pathway, as well as in the high-grade serous ovarian adenocarcinoma cell line (OVCAR-3 cells) [**119**]. The overproduction of free radicals, damaged cells, and reduced immunity worsen the case of type II diabetes, and may lead to the incidence of cancers. The antioxidant selenium nanoparticles proved to be effective, after being combined with antidiabetic therapeutics, for the management of severe cases of diabetes. Yang et al. developed metformin–selenium nanoparticles with association of tween 80 to observe its synergistic effect on cancerous cells (MCF-7). An upregulation of p38, p-ATM, and p-ATR, as well as a downregulation of cyclin-dependent kinase were noted, which caused cell cycle arrest. These processes controlled mitochondrial membrane potential [**120**].

## 6. Conclusions and Prospects

Subcellular mitochondria perform many of the most vital applications, owing to their being the powerhouse of the cell. Different potential uses, such as directing diverse signaling pathways, ATP generation, regulating mitochondrial protein synthesis, and their control of cellular events (cell proliferation, apoptosis, and cell death) in eukaryotic cells are particularly governed by mitochondria. These roles make mitochondrial participation for the management of different diseases (including diabetes, cardiac and neurological disorders, as well as tumor progression) crucial. Nanoengineered systems can offer vital applications for the management of mitochondrial-based disorders, owing to their enhanced surface area and controllable size, which can be tuned so as to easily permeate and deliver therapeutics inside the mitochondrial architecture. Stable and biocompatible metal-oxide-based nanoparticles have found promising applications in the mitigation of various ailments, including destructive cancers. They can serve as chemotherapeutics in the same manner as photodynamic therapy (PDT), sonodynamic therapy (SDT), radiotherapy (RDT), and cancer detection biomarkers. Metallic nanoparticles particularly

overexpress exogenous/endogenous reactive oxygen species, and can trigger intrinsic cell necrosis via mitophagy, as well as autophagy via other exclusive mechanisms. For instance, iron nanoparticles can cause a sharp rise in temperature inside the mitochondria in cancerous environments, trigger apoptosis, and control cancer progression, whereas zinc nanoparticles raise creatin kinase and troponin levels, and can thus damage mitochondrial DNA. Similarly, silver nanoparticles upset calcium transience through activating catabolic enzymes inside mitochondria. Multifunctional functionalized metallic nanoplatforms can more precisely and selectively target the cancerous cells, compared to nonmodified nanoparticles, and can therefore eliminate the chance of poor lysosome escape and rapid clearance. Hence, metallic nanoparticles are expected to constitute a powerful weapon for the management of a myriad of ailments and disorders. However, this approach still faces different health-related issues in clinical trials, owing to their biocompatibility and potential toxicity issues towards healthy tissues. Attention is to be paid during synthesis (preparation), animal studies, and safety assessments of nanoparticles since their oxidation state may influence the activity on mitochondria. Hence, thorough information on the modus operandi, in vivo metabolism, pharmacokinetic parameters, and toxicological aspects should be gathered in order to design safe and high-potential metallic nanoparticles for the targeting of subcellular mitochondria.

## Author Contributions

Conceptualization, review and editing, K.P. and J.M.R.; original draft preparation, S.K.M. All authors have contributed substantially to the information reported in this manuscript. All authors have read and agreed to the published version of the manuscript.

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## Conflicts of Interest

The authors declare no conflict of interest.

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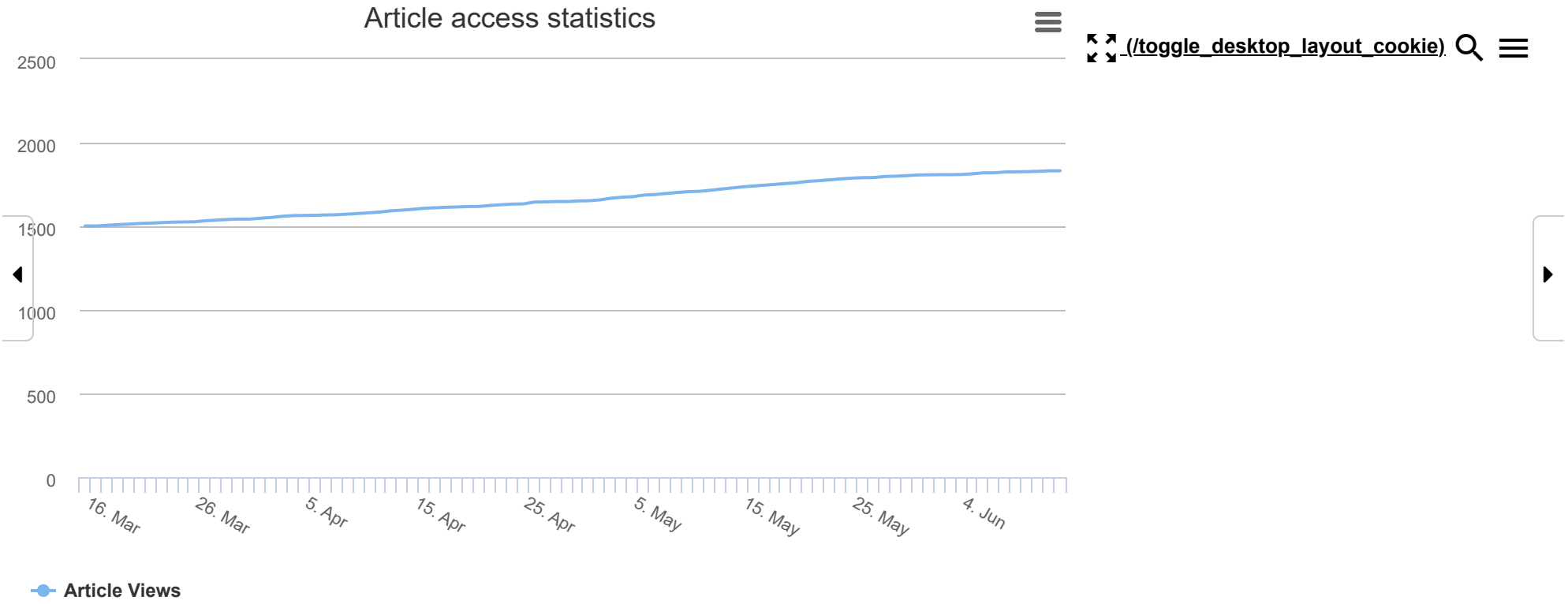
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# Nanosilver-functionalized polysaccharides as a platform for wound dressing

Review Article Published: 24 March 2023

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Polysaccharides that are naturally sourced have enormous promise as wound dressings, due to their wider availability and reasonable cost and good biocompatibility. Furthermore, nanosilver extensively applied in wound treatment is attributed to its broad spectrum of antimicrobial effects and lesser drug resistance. Consequently, wound dressings in corporating nanosilver have attracted wide-scale interest in wound healing, and nanosilver-functionalized polysaccharide-based wound dressings present an affordable option for healing of chronic wounds. This review encompasses preparation methods, classification, and antibacterial performances of nanosilver wound dressings. The prospective research arenas of nanosilver-based wound polysaccharide dressings are also elaborated. The review attempts to include a summary of the most recent advancements in silver nanotechnology as well as guidance for the investigation of nanosilver-functionalized polysaccharide-based wound dressings.

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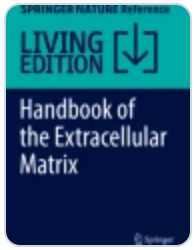
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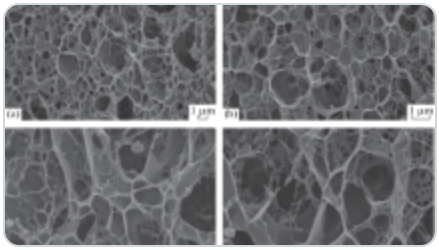
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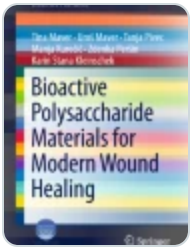

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# Data availability

***WHS:*** Wound Healing Society

***Hh:*** Hedgehog

***CS:*** Chitosan

***FDA:*** Food and Drug Administration

***MW:*** Molecular weight

***CDs:*** Cyclodextrins

***GAG:*** Glycosaminoglycan

***HSV:*** Herpes simplex virus

***NPs:*** Nanoparticles

***Ag-NPs:*** Silver nanoparticles

***NHEK:*** Natural human epidermal keratinocytes

***SSD:*** Silver sulfadiazine

***PEH:*** Polyelectrolyte hydrogels

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# Ethics declarations

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Not applicable.

## Consent to participate

Not applicable.

## Consent to publish

All the authors have approved the manuscript for publication.

## Competing interests

The authors' declare no competing interests.

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Open Access Review

# Nose-to-Brain Targeting via Nanoemulsion: Significance and Evidence

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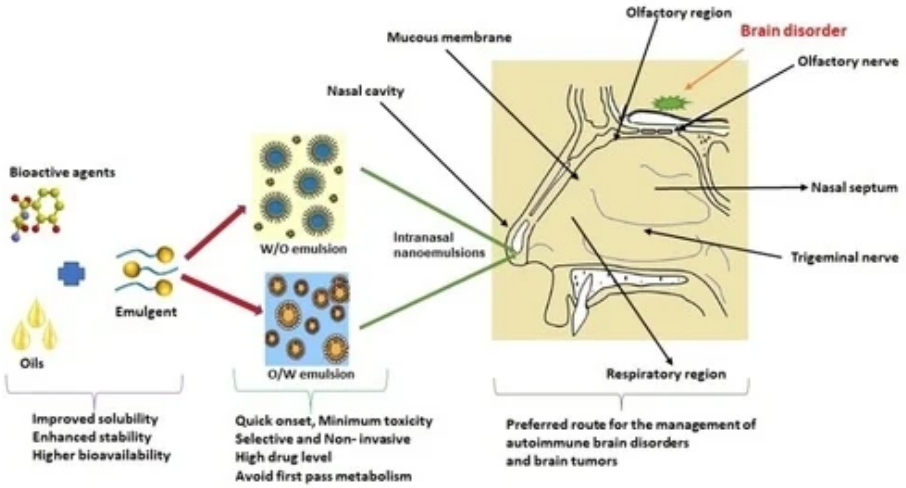
## Abstract

**Background:** Non-invasive and patient-friendly nose-to-brain pathway is the best-suited route for brain delivery of therapeutics as it bypasses the blood–brain barrier. The intranasal pathway (olfactory and trigeminal nerves) allows the entry of various bioactive agents, delivers a wide array of hydrophilic and hydrophobic drugs, and circumvents the hepatic first-pass effect, thus targeting neurological diseases in both humans and animals. The olfactory and trigeminal nerves make a bridge between the highly vascularised nasal cavity and brain tissues for the permeation and distribution, thus presenting a direct pathway for the entry of therapeutics into the brain. **Materials:** This review portrays insight into recent research reports (spanning the last five years) on the nanoemulsions developed for nose-to-brain delivery of actives for the management of a myriad of neurological disorders, namely, Parkinson's disease, Alzheimer's, epilepsy, depression, schizophrenia, cerebral ischemia and brain tumours. The information and data are collected and compiled from more than one hundred Scopus- and PubMed-indexed articles. **Conclusions:** The olfactory and trigeminal pathways facilitate better biodistribution and bypass BBB issues and, thus, pose as a possible alternative route for the delivery of hydrophobic, poor absorption and enzyme degradative therapeutics. Exploring these virtues, intranasal nanoemulsions have proven to be active, non-invasiveand safe brain-targeting cargos for the alleviation of the brain and other neurodegenerative disorders.

**Keywords: non-invasive (/search?q=non-invasive)**; **blood–brain barrier (/search?q=blood%E2%80%93brain+barrier)**; **intranasal (/search?q=intranasal)**; **nanoemulsions (/search?q=nanoemulsions)**; **neurological disorders (/search?q=neurological+disorders)**

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Graphical Abstract

## 1. Introduction

Brain diseases, including dementia, epilepsy, migraine, autoimmune disorders (Parkinson's, Alzheimer's and prion's disease), brain tumours and acute ischemic brain haemorrhages, require extensive clinical care due to a significantly high rate of morbidity and mortality worldwide [**1**]. Most of the developed brain-targeting medications relieve symptomatic brain deregulatory functions and are inefficient in providing satisfactory therapeutic responses. The major issues overlaid are (i) lipophilic blood–brain barrier (BBB), (ii) complexity of the microenvironment of the brain and (iii) abnormal protein status. Central nervous system (CNS)vessels containing arterioles and venules are regular, continuous and non-apertured. These vessels are involved in the regulation and exchange of ions and molecules throughout the braincells. The exclusive morphology of CNS vessels and the barrier function of the BBB guard the brain from the entry of antigens, toxins and pathogens. The BBB diverts blood from the interstitial fluid and serves as an efficient barricade for the diffusion of most of the actives to reach the brain receptors of the CNS. Functionally, it is a dynamic regulator that transports nutrients and checks the entry of heavy and

undesirable (lipophilic) molecules across the extracellular fluid of the brain. Lipophilic molecules with an optimum Log P (approximately 1.5–2.7) and molecularweight of 600 Daltons can freely permeate the BBB [**2**].

The brain endothelial cells (BECs) form the walls of brain blood vessels and are highly polarized in contrast to the endothelial cells of other tissues. BECs are jointed together by tight junctions that again confine the paracellular flux of ions and limit transcellular exchange between blood and brain cells, i.e., transcytosis and pinocytosis. BECs coordinate a series of metabolic, transportation and physiological functions with the interaction of several neural, vascular and neural components involved in the management of health and diseased conditions of the body. BBB-adorned p-glycoprotein efflux transporters also restrict the movement of bioactive/macromolecules and their receptor binding for a desired pharmacological response. Expression of both efflux and influx transporters between blood and brain cells ismediated via BECs. Efflux transporters (such as p-gp) that removetoxins tend to diffuse cell membranes passively, while the influx transporters are a kind of carrier that engage to deliver nutrients and ions to the brain cells [**3**]. Apart from being an active cellular self-defence barrier, the BBB strictly monitors the CNS microenvironment and communicates and acclimatises with the conduct of CNS cells in the progression of brain disorders [**4**].

These attributes of BBB create hurdles for the permeation of therapeutic or bioactive agents to reach the brain tissues, thus exhibiting obstructions to combat CNS diseases. A report of WHO healthcare statistics states that approximately 1.5 million people are sufferers of CNS disorders, including autoimmune Parkinson's, Alzheimer's diseases and schizophrenia [**5**].

Although the current drug delivery approaches have displayed a vibrant picture of effective CNS treatments with survival rates surging, still, there are unsolved issues for the complete cure/therapy of most CNS disorders. There is definitely a need for an advanced therapeutic system that enables the potential crossing of the BBB at an adequate level to attain the desired pharmacological action. The BBB limits the entry of 98% of the low molecular weight molecules and hence, drastically reduces bioavailability. A report retrieved from the comprehensive medicinal chemistry database signifies that a mere 5% of therapeutics out of 7000 with 357 Dalton molecular weight and 2.57 Log P (partition coefficient) have the potential to penetrate the BBB and exhibit potent action for mitigation of insomnia, depression and schizophrenia [**6**]. Invasive strategies, including intra parenchymal, intracranial and intra-cerebro ventricular injections, are administered for direct drug delivery to the brain. These local strategies are interlinked and emphasize the use of electromagnetic field and ultrasound approaches. These are preferred to treat psychological and neurological disorders but are painful and risky as well [**7**]. Hence, a non-invasive approach such as the nose-to-brain delivery pathway is suggested that bypasses the BBB, reduces toxicity and delivers the therapeutics at the

target site. The intranasal delivery route facilitates the direct delivery of the drug into the cerebrospinal fluid following the olfactory path [**8**].

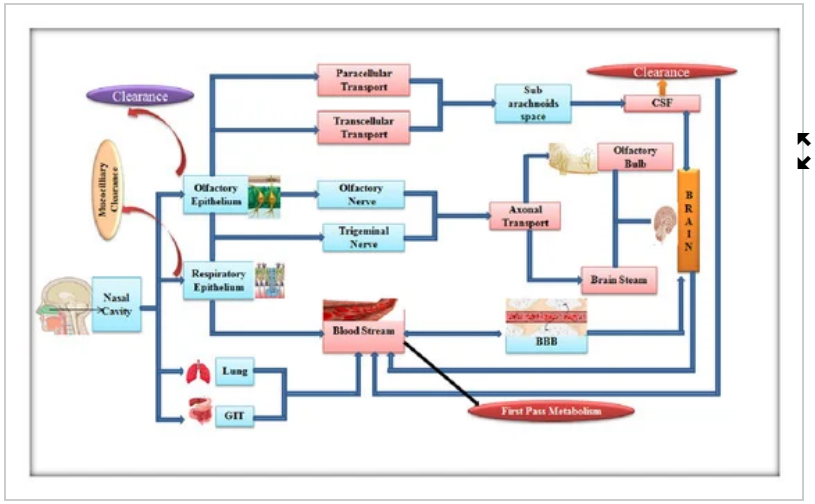
*Complexity of Nose-to-Brain Drug Delivery Path*

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The nose is an integral human olfactory/respiratory part and contains a 60 µm thick area of 1.25–2 $m^2$. The nasal septum divides the nasal cavity into the nasal vestibule, olfactory and respiratory regions. The nose entrance or nasal vestibule is covered with squamous epithelium that contains vibrissae (nasal hair) and oil glands. The respiratory region comprises the maximum surface area and holds the ciliated respiratory epithelium and vascularised nasal turbinate made up of erectile and sinusoid tissues [**9**]. The olfactory part is positioned on the rooftop of the nasal cavity and lined with olfactory epithelium (pseudostratified). Adhered olfactory nerves directly connect with CNS by circumventing the BBB. The olfactory region has a surface area of 2–10 $cm^2$. After crossing the olfactory epithelium, a therapeutic agent transports intracellularly along the associated olfactory nerve. Lipophilic molecules follow paracellular passive diffusion, while hydrophilic drugs move through a carrier-mediated transport way [**10**].

The nasal region contains two nerve terminations, i.e., olfactory and trigeminal. Both neuropathways originate from the nasal cavity at the olfactory neuroepithelium and terminate in the brain.

Interestingly, these routes are the single way that links the brain to the exterior environment and transports countless neurotherapeutic agents. A diverse range of neurotherapeutics (macro and low molecular weight) is generously distributed to the CNS via this route [**11**]. **Figure 1** portrays the typical route, including diverse transport systems and nerves for the effective delivery of therapeutic agents following the nose-to-brain pathway. Moreover, the associated blood–nerve barrier comprising the end oneurial microvessels and perineurium is involved in the regulation of the permeability of ions and molecules from both these pathways into the CNS. Hence, the blood–nerve barrier is equally important, and proper attention must be specified while designing a nose-to-brain drug delivery system. The non-invasive intranasal pathway bypasses both the BBB and first-pass metabolism. Hence, it is assumed to be superior by virtue of myriad merits, including lower dose strength, ease of administration, safety, instant therapeutic action and reduced systemic toxicity with improved patient compliance [**12**]. The focus of intranasal delivery is to transport brain-targeted therapeutics in the desired concentration at a predetermined rate. Drug metabolism, degradation and clearance can influence the efficiency of the drug at the site [**13**].




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**Figure 1.** Complex pathway involved in the transport of therapeutics through nose-to-brainroute.

The enhanced surface area of the stratified squamous naso-epithelium is extremely permeable, porous and vascularised, hence permitting fast drug absorption to occur at a smaller dose. Nasal drug delivery systems do not need any drug modification or coupling with a carrier for the distribution and effectiveness of therapeutic agents [**14**].

## 2. Nanoemulsions

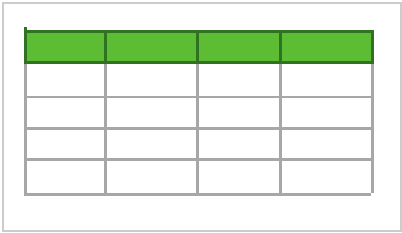
Researchers are consistently engaged in the development of promising and potential non-invasive brain drug delivery systems. To achieve the targeted CNS response, various scientific investigations have been reported that define the olfactory and trigeminal routes and successfully deliver CNS medicaments following the nose-to-brain pathway. Emulsions are colloidal systems with two distinct phases, in which one is dispersed and another is dispersion media. Their droplet or globular dimension typically varies from 200 nm to 100 µm. Countless bioactive, nutraceutical and therapeutic agents can be feasibly incorporated or encapsulated in this biphasic system for conventional and controlled effects as well [**15**]. However, conventional emulsions exhibit issues such asphysical instability (aggregation and gravitational separation) and a poor ability to control the release of the entrapped active pharmaceutical agent (API) at the target site.

Nanoemulsions are formulated via two broad methodologies, low-energy (phase inversion) and high-energy methods (ultrasonication, microfluidic, high-pressure homogenization). The low-energy method is based on phase inversion temperature

and produces a smaller globular dimension with the involvement of less energy, whereas the high-energy methods are reliant on energetic mechanical strategies and disruptive forces for the generation of smaller oil globules.

A few advanced emulsions, including multilayer emulsion, multiple emulsion, nanoemulsion, pickering emulsion and high internal phase emulsion, have been introduced for the delivery of bioactive agents. **Table 1** compiles salient features of advanced types of emulsion as drug delivery systems. However, these advanced emulsions are not cost-effective and are tedious to formulate.

**Table 1.** Salient features and drug delivery applications of advanced emulsions.



These lipophilic systems have a fine globular size, preferably in nanodimensions. These structures are well absorbed through the mucosal layer and are hence suitable for site-specific drug delivery. Among all, the nanoemulsions are the most successful among other advanced systems due to their fine size, leveraged surface area, the onset of action, biodistribution and stability. Both the o/w and w/o types of emulsions are modulated to target naso-mucosa for drug delivery across the brain tissues. Exceptionally high encapsulation of lipophilic drugs in o/w type nanoemulsion offers enhanced solubility, better absorption and improved bioavailability with minimum enzymatic degradation [**21**]. Nanoemulsions are also preferred for the formulation of mucoadhesive systems as these facilitate a long residence time and enhanced nasal absorption with limited clearance. The o/w type of nanoemulsions is better suited for brain-targeting delivery systems owing to their small size, lipophilicity and efficiency in permeating the BBB. Despite the merits offered, nose-to-brain delivery faces significant challenges and limits its frequent use. Lower bioavailability, susceptibility to enzymatic degradation and higher nasal clearance present the grey side of this route.

Moreover, mucociliary clearance, a smaller volume of the nasal cavity and its limited surface area further limit the absorption of sensitive drugs aimed to target brain tissues. Therefore, different nanoengineered mucoadhesive and in situ nanoemulgels (thermo-responsive and pH-responsive) have been designed to provide prolonged and effective drug delivery.

### 2.1. Oil and Globule Size

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Newly discovered drug molecules display poor aqueous solubility, which hence, severely affects the pharmacokinetic and pharmacodynamic characters. Oil, an integral part of nanoemulsion, resolves this issue and favours the maximum solubility of the drug entity. One can choose vegetable oil, triglycerides/diglycerides and essential polyunsaturated fatty acids depending upon the lipophilicity of the therapeutic agent. Higher oil concentration increases the globule scale of nanoemulsion and causes poor permeation across nasal mucosa [**22**]. Reports demonstrated that linolenic acid with two *cis*-double bonds and eighteen carbon monocarboxylic fatty acids couldefficiently cross the BBB, suggesting that entry of these oils in brain cells is carried out in a selective and distinct manner. Hence, it is suitable for the formulation of nanoemulsion [**23**]. For brain targeting, the lipidic component (5–20%) is selected for the formulation of the o/w type of nanoemulsion. Solubility of the oil highly matters in the selection of oil, as it must solubilize the drug molecule for efficient action at the brain target site. Usually, lipids, including cottonseed oil, coconut oil, sesame oil and soybean oil, are preferred alone to their mixture [**24**]. Further, added materials (surfactant and co-surfactant), process parameters (viscosity ratio, mixing time), rheology (shearing stress and shear rate) and type of methodology (microfluidization, phaseinversion, ultrasonication and high-pressure homogenization) decisively control the globule size distribution in nanoemulsion [**25**]. As discussed earlier, the nasal route comprises the olfactory and trigeminal pathways that are the foremost channels for brain-targeting drug delivery systems. Anatomically, the typical diameter of the olfactory axon in a human goes up to 700 nm [**26**]. Thus, the oil globular size should be kept within this limit to maintain adequate transportation and retention as well. Reports state that the smaller the oil globular dimension, i.e., 80, 100 and 200 nm, the higher the mucosal retention property for 16, 14 and12 h, respectively, in the arena of the nostril, exhibiting sluggish mucociliary clearance compared to the larger-scaled particles. Moreover, larger particles (greater than 900 nm) are also unable to reach the olfactory bulb and havepoor bioavailability inthe region of the brain [**27**].

Further, the type of oils and their properties are also significant while aiming brain targeting through nanoemulsion. The literature envisages that linolenic acid, omega-6 fatty acids, oleic acid and linolenic acids are frequently employed for the development of nanoemulsion to be delivered through the intranasal route. Ahmad et al. have developed an intranasal nanoemulsion containing amiloride (drug), oleic acid (oil) and Tween 20 and Carbitol as surfactant and cosurfactant. The selection of oil, its concentration and developed globular size played a prominent role in enhancing bioavailability in brain tissues. Outcomes suggested that an average globular size of 100 nm with a polydispersity index of 0.231 and negative zeta potential (−9.83 mV) assisted hurdle-free transportation and validated the biodistribution. Formulated nanoemulsion exhibited high drug content. i.e., ~98.38% at pH 6.4 ± 0.18. Both nose-to-brain transport (approximately 586%) and brain targeting

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efficacy (1992%) in rodents explained higher bioavailability compared to the intravenous route, thus suggesting the efficacy of the drug in epileptic sufferers [**28**].

### *2.2. Surfactant and Stability*

Surfactants not only reduce the interfacial tension between two distinct phases but also manage the stability of the biphasic colloidal system by preventing phase separation [**29**]. Further, the surfactants improve the solubility of therapeutics; alter the fluidity of the epithelium cell junctions, thus enhancing the permeation of these drugs through the nasal–mucosal pathway.

Additionally, surfactants may change the structural integrity of mucosal lining, so the selection of a concentration of surfactant is crucial while preparation of nanoemulsion aimed atbrain targeting [**30**].Reports suggest that surfactants such as phosphatidylcholine, bilesalt, chitosan, starch, Tweens (tween 60, 80), sodium dodecyl sulphate and Span (Span 60, 80),poloxamers, casein, polyethylene glycol containing block polymers and few proteins and lipids are frequently utilized for the development of nanoemulsions [**31**].

Kinetically stable nanoemulsion takes a long time to separate out in its different phases. However, diverse establishment steps, including creaming, cracking, coalescence, flocculation and Ostwald ripening, are often befall with emulsions. The globules come close due to electrostatic attraction force and form a single big entity that mediates flocculation-type destabilization. At the same time, coalescence occurs due to the merging of oil globules or water droplets. In the case of nanoemulsion, steric stabilization is stronger by virtue of the adsorbed coating of surfactant on the droplet, resulting in an enhanced repulsive maximum that checks instabilities. Formulation factors such as surfactant concentration, ionic strength, chemical configuration, solubility and temperature distinctly affect the stability of nanoemulsion. The rate of destabilization is highly concerned with increased concentration of surfactant and more diffusion of oil that reduce Gibbs elasticity. Hence, surfactant plays a critical role in a dual manner; i.e., the formulation and stability of nanoemulsion. Customized polymeric emulsifiers are suggested while preparing nanoemulsions owing to their flexibility, tailored size and hydrophobicity [**32**].

Cosurfactants assist surfactants in the reduction of boundary tension or interfacial tension up to the desired level. The mechanism or role-play of cosurfactants is similar to the surfactant; hence, an optimized concentration and desired HLB (hydrophilic–lipophilic balance) offering compound should be selected by constructing a ternary phase diagram (concentration of oil, surfactant and cosurfactant). Chiral alcohols, tween 80, polyethylene glycols 600, butan-1-ol and sorbitol are preferred as cosurfactant while formulating nanoemulsions [**33**]. Zeta potential poses a prominent role in maintaining the thermodynamic

stability of nanoemulsions. Reports demonstrate that optimum zeta potential value. i.e., ±30 mV offers an electrostatically stabilized drug delivery system. Further, the retention time in the nasal cavity was also controlled by this parameter. The nasal mucosa is adorned with negatively charged mucin at its surface; hence, positive-charge-containingnanoemulsionsaresuitableforgoodadherence in such cases [**34**]. Several of the literature reports depict most of the brain-targeted nanoemulsions with a negative charge and zeta potentialof −10 mV [**35**].

## 3. Intranasal Nanoemulsions for the Management of Brain Diseases

The intranasal pathway (olfactory and trigeminal nerves) lets the entry of various bioactive agents circumvent the hepatic first-pass effect, thus targetingneurological diseases [**36**]. Several investigations and research have suggested the vital role ofdrug-loaded nanoemulsions in the mitigation of countless brain disorders proves to be a potential alternative to oral drug delivery systems. Further, mucoadhesive polymer enriched nanoemulsion prolongs residence time and therapeutic effect by weakening rapid clearance from the nasal mucosa. Diedrich et al. (2022) developed a chitosan-coated luteolin nanoemulsion for effective brain targeting after intranasal administration in a neuroblastoma sufferer child. Obtained nanoemulsion possessed ~68 nm average particle size and positive zeta potential (~13 mV). The formulation exhibited 85.5% encapsulation efficiency and 72 h prolonged in vitro release of luteolin. Ex vivo performed Baker–Lonsdale kinetic model depicted approximately six times higher permeation across the nasal mucosa. Moreover, pharmacokinetic studies of the single dose administered intranasal nanoemulsion revealed a tentimes higher drug half-life and nearly a four times higher luteolin biodistribution in brain tissues that further suggested potential usage of developed chitosan-coated luteolin nanoemulsion for the management of brain neuroblastoma. A performed in vivo study exhibited complete inhibition of the growth of blastoma cells at a concentration of 2 μM [**37**,**38**].

### *3.1. Nanoemulsions for Neurological Disorders*

Neurological disorders include a broad range of disabilities that progressively impair the nervous system associated with vital functions of the body. i.e., mobility, sensation, coordination, reasoning, and learning [**39**]. Epilepsy, autism, Parkinson's, Alzheimer's and other neuromuscular disorders are just a few to be named in this category. These specific ailments require precise delivery of therapeutic agents inside the brain for effective results. BBB presents a formidable hurdle that limits the efficacy of conventional formulations [**40**]. For instance, acetylcholinesterase inhibitors such as rivastigmine, memantine and galantamine have the potential to manage Alzheimer's disease but possess poor brain targeting owing to theirerratic

pharmacokinetic and pharmacodynamic profiles [**41**]. Nanosized nanoemulsion and its structural architecture facilitate site-specific targeted drug release with minimum adverse effects. **Figure 2** summarizes the role of nanoemulsions in the management of brain disorders.

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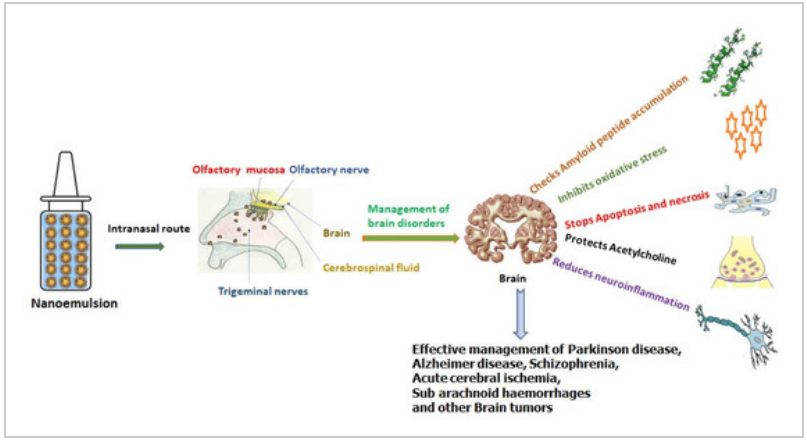



**Figure 2.** Intra nasal delivered nanoemulsion and management of brain disorders.

Jiang et al. (2022) explored herbal huperzine for the management of the neurological issue. i.e., Alzheimer's disorder. Huperzine is obtained from *Huperzia serrata*, a Chinese club moss, and has poor brain transportation. To upgrade its properties, we formulated huperzine nanoemulsion (hup-NE) modified with lactoferrin (Lf-hup-NE) that could transport the drug to the affected sites of the brain via olfactory–trigeminal nerves. Performed pharmacokinetic studies displayed greater mean residence time of modified Lf-hup-NE (4.07 h) compared to non-modified nanoemulsion (3.03 h). Similarly, Cmax and $AUC_{0-t}$ of Lf-hup-NE were also higher. i.e., ~52.29 ng/mL and ~245.09 ng/mL X h compared to developed non-modified nanoemulsions ~50.54 ng/mL and 123.63 ng/mL Xh, respectively. A rat model olfactory nerve transaction was designed to observe nanoemulsion transportation via the nose-to-brain route. Of the nanoemulsion, 50µLwas intranasal administered both in olfactory nerve transacted rats and normal rats, and in vivo fluorescence images of treated rats were collected that depicted retention of the drug in brain regions. The results confirmed successful drug absorption and transportation of hup-NE and modified Lf-hup-NE via blood circulation that implicated both direct and indirect drug delivery. P2 signals intensity of modified Lf-hup-NE was high owing to its greater efficiency of translocation in brain areas through intranasal delivery. Further, the developed modified Lf-hup-NE had the potential to inhibit P-gp efflux protein and enhanced drug concentration there. This

novel formulation can be exploited for better transportation and accumulation of herbal huperzine in brain cells and can achieve better therapeutic responses [**42**].

One of the progressive neurodegenerative motor neuron disorders is amyotrophic lateral sclerosis. It is characterized by symptoms such as the depletion of upper and lower motor neurons. A BCS class II drug, riluzole, has limited bioavailability (60%) due to poor penetration across BBB. This drug is indicated for the management of amyotrophic lateral sclerosis (ALS). Parikh et al. (2016) formulated riluzole containing o/w nanoemulsion by phase titration method. Sefsol 218 and tween 80/carbitol (1:1) were employed as oil substitutes and surfactants, respectively. The developed nanoemulsion was thermodynamically stable with a drop size of ~23 nm. Further, the formulation was free of nasal ciliotoxicity and significantly increased brain uptake of riluzole ($p < 4.1 \times 10^{-6}$) via intranasal delivery on comparing with oral nanoemulsion to the Wistar albino rats. This novel nanoemulsion has displayed a promising alternative approach for the treatment of people living with ALS [**43**].

Recently, nose-to-brain delivery of bromocriptine mesylate- and glutathione-embedded nanodimension emulsion was designed by Ashhar et al. (2022) for the effective treatment of another distinguished neurodegenerative Parkinson's disease. This fatal disorder is provoked by the generation of free radicals in neurons (dopaminergic); consequently, oxidative stress-induced neuron degradation occurs. The researchers designed intranasal dosage for containing bromocriptine mesylate and glutathione-embedded nanoemulsion to relieve oxidative stress. Performed DPPH radical scavenging analysis revealed enhanced antioxidant action due to the combined effect of both bromocriptine mesylate and glutathione present in nanoemulsion. The formulated nanoemulsion was estimated for depth of permeation with confocal laser scanning microscopy after intranasal administration, which resulted in superior penetration to the brain cells. Further, the pharmacokinetic study estimated $AUC_{0–8}$ of nanoemulsion that revealed a higher concentration of both compounds in brain regions of the Wistar rat model after intranasal administration. The nasal ciliotoxicity study in Wistar rats explained the biocompatibility of the formulated nanoemulsion. Thereafter, the biochemical study displayed a reduced level of interleukin-6, alpha tumour necrosis factor and thiobarbituric acid, which are reactive substances, and concluded that bromocriptine mesylate- and glutathione-loaded nanoemulsion has the potential to overcome oxidative stress level in persons living with Parkinson's disease [**44**].

Another chronic CNS complaint: 'epilepsy' is frequently characterized by instant senseless seizures due to neurons' electric instabilities in the brain region. BCS class II topiramate(anticonvulsant) has been employed for the clinical management of partial and generalized seizures. Its poor bioavailability on oral administration is due to poor entry across BBB. Being a substrate of P-gp transporter, we reported the limited efficacy against epilepsy. An o/w nanoemulsion was prepared utilizing

Capmul MCM C8 (2% *w*/*w*) by Patel and coworkers (2020) for the improvement of the brain delivery of topiramate. A blend of 32% surfactant and co-surfactant Tween 20 and carbitol at a ratio of 2:1 was included to customize the globular size, PDI, zeta potential and viscosity. The resulting nanoemulsion possessed a ~4.73 nm mean particle size with a stability of six months. The brain uptake efficiency of the intranasally delivered piramate contained a nanoemulsion that was quite higher ($p < 1.8 \times 10^{-8}$) compared to the orally delivered nanoemulsion. The pharmacokinetic studies in Wistar albino rats depicted enhanced bioavailability with minimum adverse effects after delivering the nanoemulsion through the intranasal route [**45**]. **Table 2** gathers recent studies on developed nanoemulsions and their applications for the treatment of various brain diseases.

**Table 2.** Recently developed nanoemulsions for the management of diverse neurologicaldisorders.

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Mucoadhesive buspirone-loaded nanoemulsion was formulated for direct delivery to the brain and modification of bioavailability after administering through an intranasal route. A total of 5% of *w*/*v* hydroxypropyl beta-cyclodextrin and chitosan hydrochloride (1% *w*/*v*) were selected for the preparation of mucoadhesive nanoemulsion. The assay resulted in a 61% improvement in bioavailability, which exhibited peak plasma concentration in rats' brains at 30 min lesser compared to bare buspirone nanoemulsion (60 min). Further, after nasal administration, buspirone–chitosan nanoemulsion exhibited 2.5 times higher $AUC_{0–480}$ in the brain (~711 ng/g) compared to I/V administration (~282 ng/g) and bare buspirone nasal formulation (~354 ng/g). Mucoadhesive buspirone–chitosan nanoemulsion revealed a high percentage of drug transport (75.77%) and targeting efficiency in the brain region [**63**]. Recently, the BCS class II drug 'melatonin' was aimed to develop a mucoadhesive nanoemulsion to enhance brain bioavailability and alleviatedepression. The formulated nanoemulsion improved the poor aqueous solubility of melatonin, and added chitosan provided a mucoadhesive property that exhibited prolonged retention time (0.641 min) in the brain region. The locomotor activity of model rats exhibited improved behavioural responses [**64**].

### *3.2. Nanoemulsions for Brain Tumour*

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Managing and treating brain tumours has always remained the most crucial and challenging task, as approximately 0.2 million clinical diagnoses of the brain and other associated CNS malignancies are reported worldwide. One of the WHO surveys stated that nearly 80%of primary brain tumours are concerned with the origin of gliomas (glial cells) [**65**]. Glioblastoma multiforme, or GBM, is the most prominent and aggressive grade IV glioma that affects nearly8%of individuals in a population of 100,000. This malignant brain tumour is highly fatal, has a very low survival rate (1 year), and requires immediate surgery and other treatments, including neuroimaging and photodynamic/radiotherapy [**66**]. Scientific reports confirmed that CD73 is accountable for the development of adenosine that is overexpressed in glioblastoma cells and hence targeted to treat this tumour in the brain region. Originally, surface enzyme CD73 was a biomarker and described as a lymphocyte differentiation antigen, and its inhibition checks glioblastoma pathogenesis [**67**]. Failure in chemotherapy may be due to impaired therapeutic action via poor permeation across BBB. i.e., microvasculature environment of the CNS.

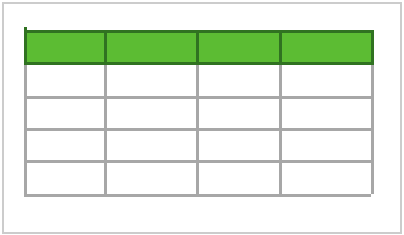
FDA-approved first-line antineoplastic therapeutic ‘temozolomide or temodar®’ is widely employed for the management of glioblastoma multiforme or GBM owing to permeation efficacy across BBB. It is a DNA alkylating drug administered orally and intravenously due to its very short half-life. However, administering high doses leads to severe adverse toxicities, including cardiomyopathy, oral ulceration, myelo-suppression and hematological issues [**68**]. To avoid these critical issues at present novel strategies such as topical implants, convection-enhanced delivery and nanotechnological-based formulations are clinically required for the management of brain gliomas. The last decade was the era of successful brain-targeted drug delivery approaches following a peculiar nasal path where trigeminal and olfactory nerves facilitate precise drug transportation due to the sole connection between the central nervous system and brain region. This non-invasive and safe route represents the quick onset of action with minimum systemic toxicity and adverse risks that comply with brain tumour sufferers. Moreover, low therapeutic doses and bypassing hepatic first-pass metabolism offer extramerits to the intranasal antineoplastic drug-delivery system.

However, half-life clearance (15–20 min) and limited volume of the formulation (25–200 µL) in a single dose pose strains and must be considered while formulating nose-to-brain delivery [**69**].

Biocompatible lipidic nanoemulsions are a highly preferred delivery system for intranasal delivery and brain targeting. The extended residing time in the nasal cavity releases the adequate therapeutic agent from the nanostructured emulsion. Bayanati et al. (2021) designed in situ emulsion-based gel of antineoplastic drug temozolomide through low energy technique for the chemotherapy of glioblastoma. The formulation bypassed BBB after delivering through the intranasal route. A suitable pseudoternary phase diagram with various quantities of triacetin, labrasol (surfactant) and transcutol®P (permeation enhancer)

was established and was added for the preparation of the nanoemulsion. The nanoemulsion contained a range of particle sizes from 19–23 nm with PDI from 0.18–0.25. A slight positive zeta potential. i.e., ~1.6 might be due to the non-ionic nature of the selected surfactant/co-surfactant. By contrast, the developed in situ gel with a blend of amphiphilic poloxamer 407 and 188 exhibited a slightly increased mean particle size (16.25 nm) and PDI (~0.35) with an acceptable pH (~6.5) that showed a compatibility with nasal mucosa without irritation. The augmented viscosity (113.57 cp) of the formulation also advocated prolonged nasal retention due to reduced mucociliary clearance. Further, in vitro release efficiencies of both nanoemulsion and its in situ gel were nearly 90% and 87%, respectively, and appeared to be sustained compared to the nasal solution after 6 h. Noticeable risen in percentage mucoadhesion was observed in situ gel (37.03%) compared to nanoemulsion (20.35%) owing to the gel-forming amphiphilic poloxamer that might have formed a noncovalent entanglement with nasal mucosa. Further, the developed in situ nanoemulsion exhibited a 1.52 times higher permeation compared to the control solution. Added labrasol and transcutol®P efficiently enhanced the solubility of temozolomide and worked as permeation enhancers across nasal olfactory–trigeminal pathways. Labrasol inhibited P-gp and acted as an efflux transporter. Both temozolomide nanoemulsion and gel with poloxamer 407 were stable during freeze-thaw cycles and performed centrifugation. Gamma scintigraphy revealed an accumulation of radio-labelled temozolomide in the brain after intranasal delivery and concluded efficient uptake to the affected site of the brain [**70**]. **Table 3** outlines the newly developed nanoemulsions for the amelioration of brain tumours.

**Table 3.** Recently developed nanoemulsion for the treatment of brain glioblastoma (data collected for last 5 years).



An amalgamation of antineoplastic paclitaxel and C (6)-ceramide-loaded oil in water nanoemulsion was developed, including a high concentration of polyunsaturated fatty acid (pinenut oil) for enhanced therapeutic action against human U-118 glioblastoma cells. The average particle size of the nanoemulsion was observed at 200 nm. Epi-fluorescent microscopy was employed for the uptake and biodistribution of rhodamine-labelled paclitaxel and nitro-benzofurazone-labelled C (6)-ceramide nanoemulsion in glioblastoma cells. On intranasal administration, the developed nanoemulsion exhibited prominently high

cytotoxicity and apoptosis within the malignant cells, thus suggesting a promising approach for the therapy of aggressive glioblastoma tumours [**76**]. Disulfiram, an alcohol withdrawal drug, is an FDA-approved antineoplastic drug that has been clinically proven in various cancerous cases, including glioblastoma. Its inclusion complex with copper ions has already gained success in the management of adenosine over-expressive human brain tumour. Qu et al. (2021) designed a novel inclusion complex of disulfiram and hydroxypropyl –β-cyclodextrin with a copper ion that augmented drug solubility and antitumour activity with increased safety in vitro.

Disulfiram is considered an active antitumour agent while complexed with copper ions. Here, disufiram is entrapped within the structure of hydroxyl propyl β-cyclodextrin; thus, the solubility and safety profile of the drug were amplified. An intense fluorescence signal was observed in the Wistar male rat brain model that indicated extreme brain targeting via the intranasal delivery of the drug. Developed inclusion complex embedded nanoemulsion promoted apoptosis after intranasal administration, thus inhibiting cell proliferation and tumour growth. Furthermore, histopathological outcomes displayed nonobvious damage to normal cells [**77**].

### *3.3. Nanoemulsions in Cerebral Ischemia*

Cerebral ischemia is a condition aroused by acute brain injury that results in inadequate blood flow in the brain region. It is also a medical emergency that, if ignored, may lead to cerebral infarction and, ultimately, permanent brain disability. Broad cerebral ischemia is categorized as global and focal. The former happens due to shock and systemic hypotension.

Structural and functional cardiac issues, including arrhythmia, mediate global ischemia. At the same time, the obstruction of arterial blood flow (thrombosis or embolism) to the brain and the irreversible neuronal loss leads to focal ischemia. Nearly 60–70% of cerebral ischemia clinically reported is due to embolism (formation of a clot) in the heart or in a large artery [**78**]. **Figure 3** portrays focal and global cerebral ischemic conditions that arise due to oxygen deficiency in the brain.

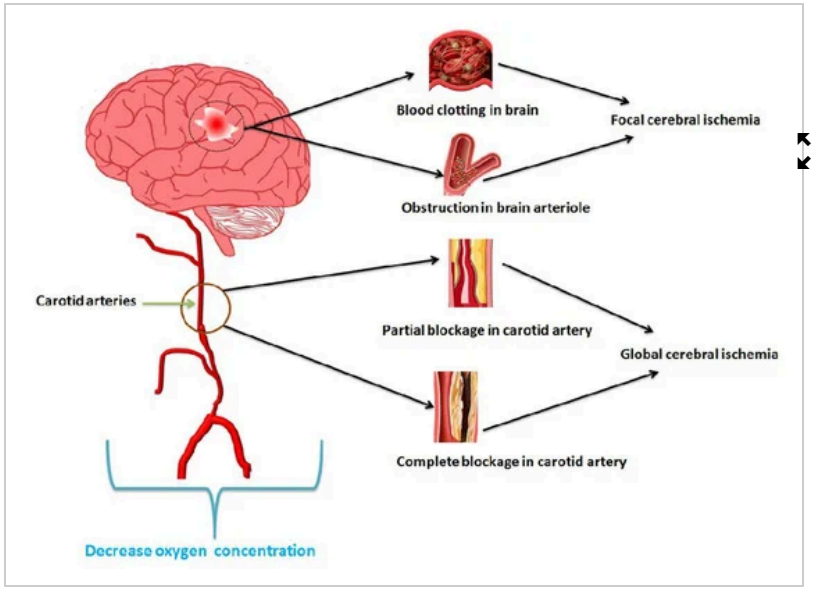



**Figure 3.** Cerebral ischemia developed due to decreased oxygen concentration in carotid arteries.

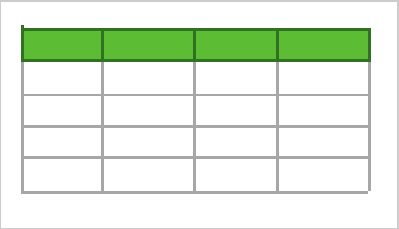
Vitamin D3 entrapped nanoemulsion was formulated using a blend of Tween 20, PEG400 and oleic acid for the improvement in cerebral ischemia. The targeting potential of formulated nanoemulsion was analysed through gamma scintigraphy in a rat model. The developed nanoemulsion possessed an average globular size of ~49.29 nm with a positive 13.7 mV zeta potential. The stable thermodynamic preparation was found to have a permeation coefficient of 7.8 cm/h after 3 h in sheep nasal mucosa. Further, analysed radiometry and gamma scintigraphy displayed an efficient percentage deposition of $^{99m}$Tc-vitamin D3 nanoemulsion across nasal mucosa compared to IV-administered solution (0.8%). The magnetic resonance imaging on the ischemic rat model confirmed the promising antioxidant action of developed nanoemulsion through the intranasal pathway [**79**].

The neuroprotective property of antioxidant safranal was explored in a focal ischemic model that contained major issues, including neurobehavioral loss, hippocampal cell loss and release of oxidative stress markers. Sadeghnia et al. (2017) developed a safranal-loaded nanoemulsion for intranasal delivery to overcome the above-said issues related to the cerebral ischemic rat model. The study significantly demonstrated a reduction in neurological, hippocampal cell loss and thiobarbituric acid reactive substances (TBARS). Moreover, marked increases in antioxidant capacity and SH content were also observed, suggesting a potential role of antioxidant herbal safranal in neuroprotection, free radical suppression and the treatment of

cerebral ischemic reperfusion [**80**]. Antioxidant thymoquinone has poor aqueous solubility and bioavailability. Its neuroprotective action and potential to ameliorate cerebral ischemia have attracted researchers to explore the design of nanoemulsion. Mucoadhesive thymoquinone-loaded nanoemulsion was prepared via the ionic–gelation method. The formulated system comprised small globules (average size ~94.8 nm) with negative zeta potential (−13.5 mV). Viscosity and percentage drug content were reported as~110 cp and 99.86%, respectively.

The developed bioanalytical method displayed comparatively enhanced biodistribution and brain bioavailability after nasal route delivery than the intravenous pathway. Thymoquinone brain targeting potential was observed up to 89.97% after post-intranasal delivery of nanoemulsion. A performed neurobehavioral activity on the middle cerebral artery occlusion-persuaded ischemic rat model revealed the potential for antioxidant thymoquinone-embedded nanoemulsion to treat cerebral ischemia [**81**]. **Table 4** lists some intranasal nanoemulsions applied for the control of cerebral ischemia.

**Table 4.** Recently reported nanoemulsions for the management of cerebral ischemia.



### *3.4. Nanoemulsions in Brain Infections*

Brain infections may occur in the regions of the cerebrum, cerebellum, spinal cord and associated nerves. In this context, encephalitis, meningitis and abscess are declared as medical emergencies and their long-term sequelae may result in substantial mortality. Bloodborne pathogens, head trauma and skull fractures can mediate the opening of tight junctions between the CNS and other nerves. Further, neurosurgical procedures and medical device implantation (exterior drainage tube, shunt) may cause infection due to microbial colonization and thus behaveas the foci of infection [**86**]. Rinaldi et al. (2020) suggested a successful nose-to-brain intranasal delivery route for the management of fatal meningitis and encephalitis. Essential oils composed of nanoemulsions (mean average diameter 100 nm with PDI 0.2) were chosen to transport at the infected site of the central nervous system. In this context, antibacterial oils extracted from *Thymus vulgaris* and *Syzygium aromaticum* were individually incorporated in the chitosan-coated nanoemulsions (C-TV-NEs and C-SA-NEs) and investigated

against multidrug-resistant methicillin-susceptible *S. aureus* and carbapenem-resistant *A. baumannii* and *K.pneumonia*. Nanoemulsions, i.e., TV-NEs and SA-Nes, exhibited negative zeta potentials as −40 mV and −30 mV, respectively, that were converted into positive charges after chitosan coating by virtue of electrostatic interaction. However, the mean droplet size and PDI were amplified after the coating of the mucoadhesive chitosan polymer.

Intranasally administered nanoemulsions appeared more suitable for the potential curing of brain infections caused by Gram-negative bacteria compared to the intravenously delivered high dose of the formulation, presenting an efficient alternative therapy for the cure of serious meningitis and encephalitis [**87**]. A blend of essential oils is widely used to manage different virus infections caused by human rhinovirus, bovine rotavirus, herpes virus, H5N1 and HIV. Essential oils, such as thyme oil, eucalyptol, borneol, alpha terpineol and sage oil, are reported to be included in the formulation of nanoemulsion. Their mixture initiates nucleoprotein trafficking abnormalities in the surface protein of the virus, hence interfering or masking the virion envelope and blocking virus internalization [**88**]. A myriad of viruses, including poliovirus, rabies, herpes simplex and HIV, can reach the CNS through an intraneural path, causing encephalitis and brain abscesses, whereas meningitis is spread through bacterial pathogen at the subarachnoid space. Any breaches or damages (necrosis, microhemorrhage) of the BBB mechanical obstruction (infected RBCs, WBCs or platelets) and excessive production of cytokines disturb the structural architecture (tight junction) of BBB that led to the brain infection. Several reported pathogens, including a wide range of bacteria, fungi, viruses, cerebral malaria and spirochetes, are extensive causes of CNS or brain infections [**89**].

The immunologically privileged central nervous system (CNS) remains the residing site for human immunodeficiency virus 1. Poor permeability across the tight junctions of BBB leads to inadequate and limited delivery of most of the anti-HIV therapeutics. Therefore, nanotechnology-based formulations have attracted medical scientists and researchers to design novel strategies for the management of neuro-AIDS. Saquinavir mesylate, a protease inhibitor, has been explored as an antiretroviral drug, but due to poor solubility and bioavailability (4%), its use is limited. O/W intranasal nanoemulsion containing saquinavir mesylate was formulated via a spontaneous emulsification method to enhance CNS bioavailability. The developed nanoemulsion was thermodynamically stable on analysing through freeze–thaw and heating–cooling cycles. The obtained low PDI (0.078) and smaller globular diameter (176.3 nm) indicated the development of monodispersed nanoemulsion that would be suitable for brain targeting via intranasal delivery. Estimated optimum zeta potential (−10.3 mV), pH (5.8) and refractive index (1.412) depicted good stability, non-irritancy and the compatibility of nanoemulsion. Higher-percentage drug permeation and permeability coefficients after 4 h on intranasal administration were observed as 76.96% and 0.51 cm/h, respectively, compared to the pure drug (26.73%, 0.17 cm/h).

The in vivo study in sheep nasal mucosa displayed higher drug permeation and biodistribution rate of nanoemulsion on comparing with its suspension. Further, the cilia-toxicity study depicted no prominent adverse action on the sheep nasal mucosa. Gamma scintigraphy images demonstrated higher drug transportation region in the rat brain that concluded its efficiency for treating neuro-AIDS by reducing the devastating viral load from reservoir sites [**90**].

### *3.5. Nanoemulsions in Migraine and Cerebral Vasospasm*

Another neuron-disabling disorder, ‘migraine’, is characterized by intense throbbing headaches in one of the halves of the brain. One of the surveys demonstrated that migraine is the sixth most prevailing brain disorder and affects approximately 15% of sufferers worldwide [**91**].

Recurrent episodes of pain in unilateral headaches are allied with other visual, auditory and autonomic nervous disorders. Mostly, females are more affected due to their poor lifestyle. The pain is so intense and unbearable that the patient needs quick relief from it [**92**]. Poor solubility, erratic absorption, inadequate permeation and fewerpenetration properties of most of the conventional therapies across BBB led to poor efficacy in the brain region. Delayed gastric emptying, first-pass metabolism, slow onset of action, nausea and vomiting and the intake of high doses are undesirable issues associated with anti-migraine drugs if given orally.

The intranasal route is more effective for the delivery of anti-migraine therapeutics owing to the involvement of olfactory and trigeminal nerves. These anatomical features are potentially involved in the greater distribution of drugs without facing issues of first-pass metabolism [**93**].

Rizatriptan, a serotonin 5HT 1B/1D receptor agonist, exhibits only a 40% bioavailability upon oral delivery. An intranasal preparation of rizatriptan benzoate nanoemulsion improved brain tissue deposition and offered a non-invasive alternative approach for brain targeting. Biodistribution through the olfactory pathway directly delivers the drug to the central nervous system [**94**]. Another well-tolerated anti-migraine drug, zolmitriptan, also possesses low bioavailability after oral administration. Ahigh-dose prescription in conventional preparation causes serious side effects, including irregular heart rhythm, stroke and Raynaud’s disease. Ebtsam et al., 2017 formulated a mucoadhesive nanoemulsion for the direct nose-to-brain transportation of zolmitriptan. The improved and quick onset of action is desired to alleviate acute migraine fulfilled with this formulation. An added 0.3% of chitosan acted as a mucoadhesive agent in the preparation and increased the residing time and drug permeation across associated nasal mucosa, hence assisting the transport of the drug to the brain tissues. Performed in vivo studies displayed shorter Tmax and higher $AUC_{0-8}$ of intranasally administered nanoemulsion compared to intravenous or

nasal zolmitriptan solution [**95**]. Sumatriptan has been widely employed for the management of severe and painful migraine for decades. High hydrophilicity and less mucoadhesive features limit its application through the nasal route. Ribeiro et al. 2020 have developed a novel nanoemulsion containing sumatriptan, copaiba oil and organic biopolymers. i.e., alginate, pullulan, xanthan and pectin. Mean particle size, PDI and zeta potential of nanoemulsion were observed as approximately 120 nm, 0.2 and −25 mV, respectively.

The developed alginate-based nanoemulsion exhibited long term storage stability (1 year) due to optimised zeta potential. In vitro study depicted extended release from sumatriptan-loaded alginate nanoemulsion upto 24 h. The in vivo toxicity in the zebrafish model revealed no evidence of mortality and other cardiac toxicity and did not disturb spontaneous changes in zebrafish larvae, hence showing a promising alternative approach for the alleviation of brain diseases, including migraine [**96**].

Cerebral vasospasm is defined as the temporary narrowing or thinning of cerebral arteries. More often, subarachnoid haemorrhage and traumatic brain injuries result in cerebral vasospasm.

The appearance of new focal neurological signs, inflammation, microcirculatory failure, bipolar disorders and loss of consciousness re-associated aspects are addressed with subarachnoid haemorrhage [**97**]. Cerebral vasospasm is the leading cause of mortality if not identified and treated immediately. It typically affects concerned blood vessels at the skull base that influences arterial contraction, blood pressure and blood viscosity. **Figure 4** defines different causes of cerebral vasospasm and its different signs and symptoms that have appeared in the sufferer.

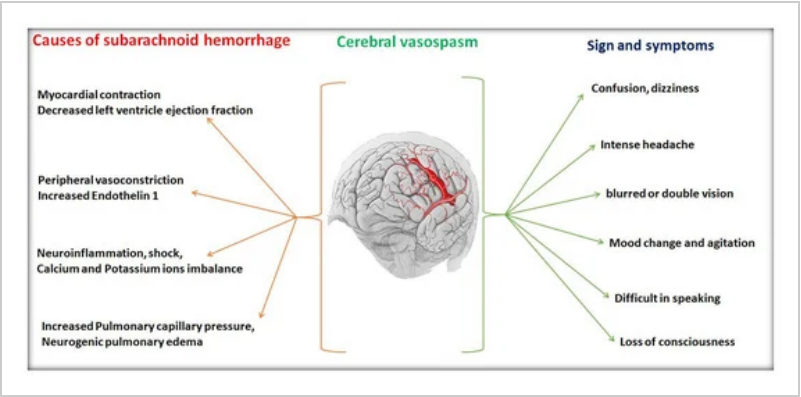



**Figure 4.** Various causes and symptoms of cerebral vasospasm.

Endovascular therapies are recommended for the management of severe vasospasm cases. However, the radiological and computed tomography evidence suggested that approximately 20% of cases of vasospasm can be treated via performing angiograms within a week of aneurysmal rupture. Some clinical reports also described that the level of nitric oxide was found to be decreased due to vasoconstrictor endothelin and extra vascular oxyhaemoglobin [**98**].

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Cerebral vasospasm is often evident after aneurysmal subarachnoid haemorrhage. However, in some instances, it is observed after skull surgery associated with intractable epilepsy and amygdala-hippocampectomy. Carbamazepine 400 mg is recommended to overcome developed issues in this case. Dhobale et al., 2018 formulated carbamazepine nanoemulsion for efficient brain targeting via the intranasal route. A spontaneous emulsification method was employed for the formulation of nanoemulsion utilizing Capmul MCM (oil) and TWEEN 80/PEG-600 (3:1) as surfactant and co-surfactant, respectively. The developed nanoemulsion contained a smaller globular size of ~71.7 nm with a 0.256 ± 0.002 polydispersity index. The in vivo study depicted efficient drug distribution in 5 h [**99**]. Survival from cerebral vasospasm or aneurysmal subrachanoid haemorrhage was improved. FDA-approved nimodine is a calcium channel blocker and is widely prescribed clinically to treat subarachnoid haemorrhage. In this series, fasudil (Rho-kinase inhibitor), nicardipine (calcium channel blocker), statins (hypolipidemic), clazosentan (endothelin receptor antagonist), cilostazol (platelet aggregation factor and heparin (anticoagulant) has also been added as effective therapeutics in clinical practice [**100**].

Ahmad et al. have discussed a novel bioimaging tool. i.e., targeting probe that is based on an on–off signal and significantly traces the translocation of the therapeutic agent throughout the nose-to-brain pathway. A cargo was developed containing environmentally responsive dye P2 and P4, caumarin 6 and DiR conventional probes. Translocation of nanoemulsion (prepared with Labrafac®CC/ WL1349 and solutol®HS15) after intranasal administration was evident either via bioimaging or through histopathological examination in rats. Outcomes concluded that nanoemulsions (coated with chitosan and naked) with a mean particle size of 100 nm exhibited higher retention duration in the nasal cavity with slower clearance compared to larger particles. Weak P2 and P4 signals were also observed in the region of the olfactory bulb for coated nanoemulsions of particle size 100 nm. Moreover, nanoemulsion particle sizes of more than 900 nm were unable to reach the olfactory bulb. Signals obtained from caumarin 6 and DiR represented significant transportation of nanoemulsion in the brain region.

The importance of particle size and their cytoprotective efficiency under the circumstances of oxygen–glucose deprivation and reoxygenation were also signified by Varlamova and coworkers in 2022. It was reported that the average particle size of selenium (50 nm) could induce calcium ion responses and inhibit apoptosis in the brain cortex cells. At the same time, upon

increasing particle size, i.e., 100 nm and 400 nm, exhibited induction of calcium ion oscillation and mixed pattern of calcium signals, respectively. Hence, cryoprotective action under oxygen–glucose deprivation and reoxygenation conditions can be provided at the size range 50–400 nm that is required to protect brain tissues from ischemic conditions through modulation of the calcium ions signal system of astrocytes [**101**,**102**].

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## 4. Future Prospects and Conclusions

Although intranasal nanoemulsions successfully deliver therapeutics with minimum side effects at the site, several formulation aspects (type of oil, polymer and surfactant/cosurfactant), process stabilizing parameters (methodology, temperature, rheology, particle size) and pharmacokinetic issues (solubility, absorption, bioavailability) always create challenges for the competent treatment of brain disorders. High molecular weight containing hydrophilic therapeutics poses problems for nanoemulsion formulation. Enormous work on the preparation and evaluation of intranasal nanoemulsions has been reported within 5 years for the management of myriad brain-associated ailments. Nanoemulsions prepared with mucoadhesive polymers and in situ nanoemulgels confine fast nasal clearance and improve residing time and permeation of bioactive across the nose-to-brain pathway.

Mucoadhesive starch-based polymers (potato starch, wheat starch, rice starch), gaur gum, xanthan gum and tragacanth are not only safe, cost-effective and eco-friendly but also are proven natural components that make intimate contact between nasomucosal membrane and nanoemulsions system. Similarly, in situ nanoemulgels embedded with nanocarriers comprise stimuli-sensitive (pH, temperature, ionic concentration) ingredients that respond to the environment of the nasal cavity and augment the viscosity of the nanoemulsion system. Therefore, surged biodistribution and improved contact time across nasomucosal membranes overcome shortcomings of nanoemulsions and offer a safe and desirable benchmark for targeting brain diseases. Although mucoadhesive and in situ nanoemulgels are fascinating strategies, formulation aspects (osmolarity, pH, buffer capacity, viscosity, drug concentration) and physiological parameters (absorption, nasal blood flow, mucociliary clearance, enzymatic action, pathophysiological issue) are still to be monitored for the effective delivery of therapeutics via the nose-to-brain route.

Currently, nose-to-brain targeted rationally designed nanoemulsions have been proven as a successful alternate approach for the precise alleviation of countless brain-associated disorders. Adequate endothelial cell internalization by nanoemulsion via transcytosis and endocytosis mechanisms mediate desirable therapeutic effects with minimum adverse effects. Associated

olfactory and trigeminal pathways facilitate biodistribution and bypass issues with the BBB barrier and drug first-pass metabolism. Exploring these virtues, intra-nasal nanoemulsions have proven brain-targeting cargos with their broad array of applications. Recently, targeting probes that contain environment-responsive dyes have been employed for the tracking of bio translocation of the nanoemulsion via fluorescence bioimaging technology. This strategy validates the efficacy of the nanoemulsion with evidence.

## Author Contributions

Conceptualization, review and editing: K.P., original draft preparation: S.K.M. All authors have read and agreed to the published version of the manuscript.

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## Data Availability Statement

No new data is generated.

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## Conflicts of Interest

The authors declare no conflict of interest.

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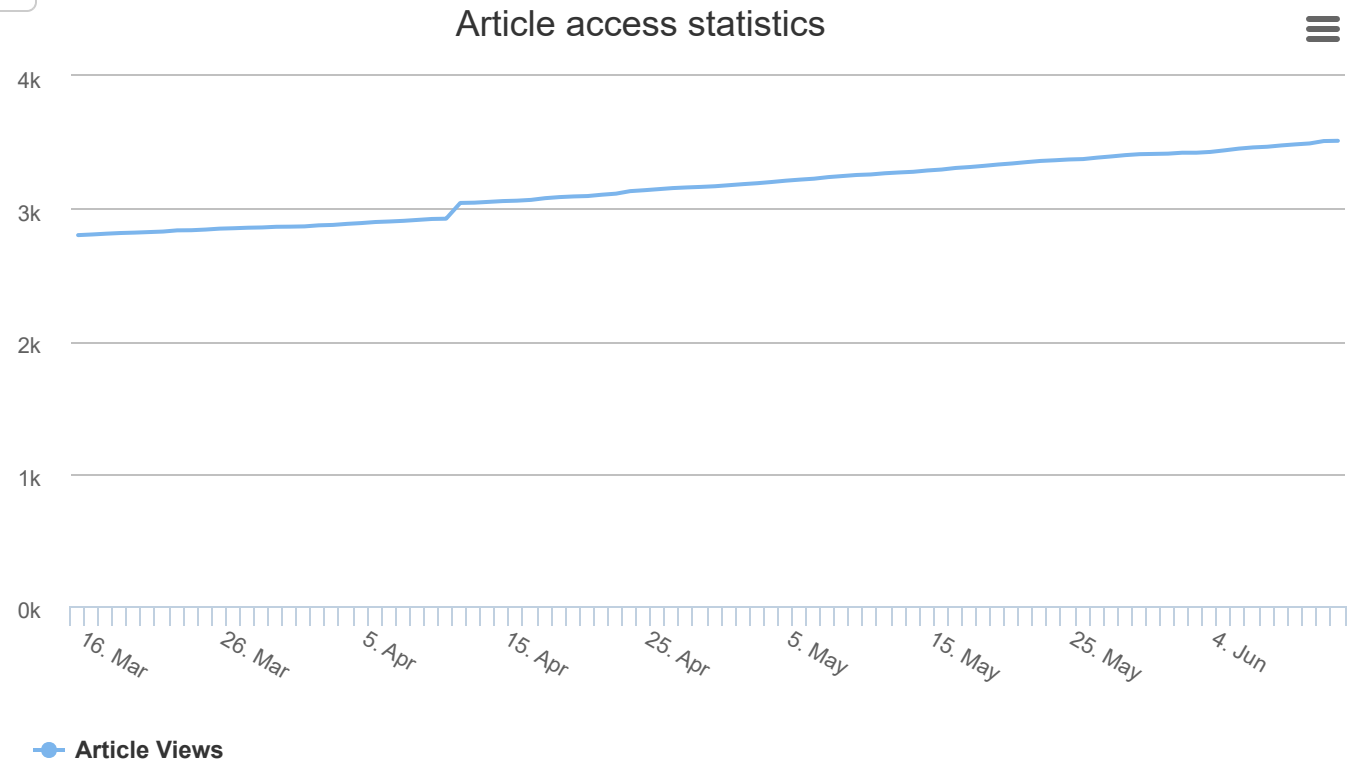
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# Codelivery of Phytochemicals with Conventional Anticancer Drugs in Form of Nanocarriers

*Pharmaceutics* **2023**, *15*(3), 889; https://doi.org/10.3390/pharmaceutics15030889 (https://doi.org/10.3390/pharmaceutics15030889)

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## Round 1

### *Reviewer 1 Report*

The authors introduced the DDS to co-deliver phytochemicals and conventional anticancer drugs. It is suitable for pharmaceutics. But please address the following points.

1. Please discuss the advantage of co-delivery nanosystem, such as unifying pharmacokinetics of different drugs.

2. For small molecule combination therapy, always more side effects will be observed in clinic. This is another reason to use co-delivery nanosystem.

3. Any example of nanosystem in clinic is co-delivery of phytochemicals and conventional anticancer drugs?

4. Please give some specific figures as typical co-delivery examples. By the way, please include another phytochemical, colchicine. There is some reports on co-delivery (10.1002/adma.202105254).

5. The authors should discuss the common advantages of DDS, such as functionality (10.1021/jacs.0c09029).

6. It is better to discuss more deeply on how phytochemical can affect the co-delivery system, particularly using some specific anticancer drugs, such as cisplatin (10.1016/j.jconrel.2022.03.049). The authors can discuss their own opinions in concluding remarks.

### *Author Response*

**Reviewer 1**

1. **Please discuss the advantage of co-delivery nanosystem, such as unifying pharmacokinetics of different drugs.**

Ans: Thank you for insightful and valuable suggestion of reviewer. We have incorporated the above point in manuscript as follows:

The differences in pharmacological fate and pharmacokinetic profile of individual agents may cause serious side effects and systemic toxicity. The codelivery in nanocarriers enclosed the pharmacokinetics of the drugs which enables the unifying of pharmacokinetic properties of the codelivered drugs, increased biodistribution time, and enhanced selectivity to the tumor. The remarkable advantage of nanocarriers is the ability to release therapeutic agents in a controlled manner in terms of location, time, amount, and sequence. Therefore, co-delivery systems can be considered potential candidates to maximize treatment efficiency, minimize side effects, and improve the pharmacokinetic profile of combined therapeutic agents. Furthermore, they provide controlled, sustained, and targeted release of the embedded drugs. The half life of the encapsulated drugs can be increased in the blood circulation.

2. **For small molecule combination therapy, always more side effects will be observed in clinic. This is another reason to use co-delivery nanosystem.**

Ans: Thanks for providing insightful and valuable suggestions. Your point is absolutely correct as we have perceive the idea about the same by keeping in mind your above mentioned statement also. The codelivery of phytochemicals with chemotherapeutic drugs is suboptimal due to various physiochemical and pharmacodynamic characteristics of different drug molecules, lack of optimistic dosing and scheduling of various drugs in codelivery, hydrophobicity of the drug, first-pass effect, low aqueous solubility, poor bioavailability. Moreover, codelivery of small drug molecules shows more adverse effects clinically. These hindrances associated with the codelivery of chemotherapeutic drugs with phytochemicals prompted the development of novel drug carriers which mainly include nanotechnology-based drug carriers termed nanocarriers.

We have incorporated above point in the manuscript under Section 6.

3. **Any example of nanosystem in clinic is co-delivery of phytochemicals and conventional anticancer drugs?**

Ans. We have also worked on the same at the time of writing the manuscript. But, after going through extensive literature review we have not found any nanosystem for codelivery of phytochemicals with conventional anticancer drugs clinically. However various nanosystem for codelivery of conventional anticancer drugs are available clinically which is given in below mentioned table for your reference purpose.

| Name | Composition | Status | Indication |
|---|---|---|---|
| CPX-1 | Irinotecan and floxuridine (1:1) Liposome | Phase 2 | Colorectal cancer |
| DPX-0907 | Liposomal 7 tumor-specific HLA-A2-restricted peptides and a polynucleotide adjuvant | Phase 1 | Ovarian, breast, and prostate cancer |
| MM-302 | HER2-targeted liposomal doxorubicin (PEGylated) | Withdrawn | Breast cancer |
| Dher2 + AS15 | Truncated HER2 protein in combination with the immunological Liposomal AS15 adjuvant | Phase 2 | Breast cancer |

4. **Please give some specific figures as typical co-delivery examples. By the way, please include another phytochemical, colchicine. There is some reports on co-delivery (10.1002/adma.202105254).**

Ans: Thank you for valuable suggestions. We have gone through suggested article which is very impactful and knowledgeable. We have incorporated colchicine in phytochemicals for codelivery in Section 5 of manuscript and Figure 4.

5. **The authors should discuss the common advantages of DDS, such as functionality (10.1021/jacs.0c09029).**

Ans: Thank you for your insightful suggestion. This will definitely improve our manuscript. As per your suggestion, we have discussed about the functionality of the nanocarriers as given in suggested article as follows:

Functionalization of nanocarriers employing stimuli responsiveness like pH, temperature, time and decoration of nanocarriers surface with specific legends can be provided which elicit prolonged drug retention at targeted site as well as improved cellular uptake of targeted drugs. The functionalization of nanocarriers leads to increase in bioavailability of the targeted drugs. The ligands employed for functionalization includes antibodies, aptamers, small molecules, peptides etc

6. **It is better to discuss more deeply on how phytochemical can affect the co-delivery system, particularly using some specific anticancer drugs, such as cisplatin (10.1016/j.jconrel.2022.03.049). The authors can discuss their own opinions in concluding remarks**.

Ans: As per your suggestions we have incorporated text regarding some specific anticancer drugs such as paclitaxel, cisplatin, doxorubicin as following:

In a study, codelivery of conventional anticancer drug paclitaxel with naringin employing polymeric micelles improved in vitro cytotoxicity against MCF-7 breast cancer cells and enhanced internalization of paclitaxel. In this, naringin serves as chemosensitizer, improving the lethal effect of paclitaxel in prostate cancer synergistically. In another study, codelivery of doxorubicin with curcumin improved anticancer potential of doxorubicin along with reduction in adverse effects. Till date, numerous conventional anticancer drugs are codelivered with plant derived compounds to improve their efficacy.

As per your suggestions, following text has been incorporated in conclusion.

Recently the codelivery of conventional anticancer drugs with phytochemicals has paid attention to the treatment of cancer but the occurrence of overlapping, multiple, and occasionally unanticipated adverse effects is a great challenge in codelivery of anticancer drugs. On this subject, encapsulation of drugs in nanocarriers provides the safer combination

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*Reviewer 2 Report*

The authors generally wrote an excellent paper on phytochemicals and anti-cancer drug delivery. It would be nice to clarify the configuration and publish it after major revision.

1.In the title " in form of nanocarriers" Are they both carriers?

2.It is an undeniable fact that plant-derived compounds have low anti-cancer efficacy (compared with anticancer drugs). It's not just issues like solubility (To be drugs). It is better to write the contents in the text and abstract.

3. It would be better to drastically cut Chapter 2 (Aetiology, pathogenesis, and metastasis of cancer) in half. It is difficult to see that it is directly related to the text.

4. Chapter 3 needs to be rewritten in relation to "phytochemicals". Can phytochemicals solve the drawbacks described in Chapter 4?

5. Figure 1 also needs to be modified (related to "phytochemicals" and "nanocarrier?"). Information on the occurrence of simple cancers is not required.

6. Chapter 5 is good, but it is needed to break up the paragraphs and clarify the content for the potential readers.

7. Check the grammar of the words in Figure 2 again.

8. Overall, I think it will help to understand if I divide the paragraphs and describe them.

9. It would be good to reflect the classification (nanocarriers) in Chapter 6 in Table 2 as well. The contents of Table 2 are good, but the classification is awkward. For example, What does simple nanoparticle (Table 2) mean (not SLN?, NLC?) ?

*Author Response*

**Reviewer 2**

**1.In the title " in form of nanocarriers" Are they both carriers?**

Ans: Both (anticancer drugs and phytochemicals) are the drug moieties which are encapsulated in nanocarriers in combination to provide improved anticancer efficacy.

**2.It is an undeniable fact that plant-derived compounds have low anti-cancer efficacy (compared with anticancer drugs). It's not just issues like solubility (To be drugs). It is better to write the contents in the text and abstract.**

Ans: Yes, Your above mentioned statement is absolutely correct. Plant derived compounds have low anti-cancer efficacy when compared to conventional anticancer drugs. We have incorporated the following point in text as well as in the abstract as per your valuable suggestion. Your suggestion will definitely improve our manuscript.

Various preclinical studies have demonstrated that the combination of phytochemicals with conventional anticancer drugs is more efficacious than phytochemicals individually to treat cancer due to the fact that plant derived compounds have low anticancer efficacy than conventional anticancer drugs. Moreover, phytochemicals suffer from poor aqueous solubility and reduced bioavailability which must be resolved for efficacious treatment of cancer

3. **It would be better to drastically cut Chapter 2 (Aetiology, pathogenesis, and metastasis of cancer) in half. It is difficult to see that it is directly related to the text.**

**Ans: Thank you for valuable and insightful suggestions of reviewer. We have cut the chapter 2 and tried to relate it with the text.**

The terms "carcinogenesis," "oncogenesis," and "tumorigenesis" refer to the process that causes tumours to form (the "pathogenesis of cancer") and the agents responsible for causing cancer are carcinogens. Ever since the first carcinogen was discovered, a growing number of substances have been linked to the genesis of cancer. Because of recent enormous advancements in the fields of molecular biology and genetics, there has been an even bigger collection of knowledge regarding the pathogenesis of cancer[17]. According to WHO, it is reported that nearly 10 million deaths occurred in 2020 and about one in six deaths[18]. Nearly one-third of cancer patients' deaths occurred by consuming tobacco, and alcohol, less consumption of fruits and vegetables in their diet, obesity, and lack of exercise. Human papillomavirus (HPV) and hepatitis infections are the major cause of cancer, with approximately 30% of cancer cases reported in lower and lower-middle countries. Breast, lung, colon, rectum, and prostate cancers are the most prevalent types of cancer[19]. But fortunately, many types of cancer are curable with the right diagnosis, early detection and care.

The ability of cancer cells to grow more quickly than healthy cells is one of their defining characteristics. The majority of conventional anticancer drugs are made to target these quickly proliferating cells and stop, kill, or slow down their proliferation. Nevertheless, these anticancer drugs also harm or destroy healthy, normal cells. The patient will consequently have serious adverse effects, and the effectiveness of the therapy will be limited or diminished[20].

The development of a normal, healthy cell into a tumour cell is known as carcinogenesis which involves involving numerous genes and genetic changes. Carcinogenesis is a multiplex process encompassing origination, promotion, and progression[21]. The first step involves the beginning of a permanently altered cell and is frequently linked to a mutation and several start pathways. The initial altered cells grow and manifest as a visible mass of cells during the second stage, which is most likely a benign lesion. Epigenetic elements that influence the proliferation of the started cells are undoubtedly present during the promotion stage. It is not well understood exactly how the second stage of carcinogenesis works.

Mostly benign or non-cancerous cells, or occasionally pre-cancerous cells, are the end result of promotion. When these benign cells transition into neoplastic cells, they experience a few additional genetic changes. The third and final stages of carcinogenesis, which involve the development of malignant tumours from benign non-cancerous tumours, are distinct from the first two steps[22] .

Stem cells play a crucial role in the beginning of carcinogenesis owing to variety of physical, chemical, or biological stimuli, including viruses. The sequential steps are crucial in the malignant transformation of preneoplastic cells because such initiated cells would then be exposed to a promotional factor to accelerate the full neoplastic cell creation[23]. A multicellular animal's carcinogenesis process results from numerous cellular chemical, physical, biological, or genetic alterations. Although mutation is the primary cause of carcinogenesis, a number of additional variables also contribute to its growth. The use of either conventional anticancer drugs or plant derived compounds are available option to reverse or capture the process of carcinogenesis which influence the carcinogenesis process at each stage of cancer development.

4. **Chapter 3 needs to be rewritten in relation to "phytochemicals". Can phytochemicals solve the drawbacks described in Chapter 4?**

**We have discussed the progression of conventional anticancer drugs in chapter 3 followed by hindrances in cancer treatment by these conventional anticancer drugs in chapter 4. In chapter 5, we have written about the treatment of cancer using phytochemicals as follows:**

Because of the limitations of conventional chemotherapeutic drugs, there is an urgent need for novel cancer treatment. Recently plant-derived agents namely phytochemicals have drawn the attention of researchers as a new treatment modality for cancer owing to various attributes of less adverse effects, action through multiple pathways, and cost-effectiveness [2],[10]. From ancient times, humans have made great use of plants for the treatment of various kinds of ailments including cancer[41]. Since mostly available conventional chemotherapeutic drugs like vincristine, vinblastine, and paclitaxel are plant-derived, the attention of researchers turned towards phytochemicals for the treatment of cancer[42].

According to studies, there are over 250000 plant species in the plant kingdom, but only about 10% of those have been proved their potential as a treatment option for various kinds of diseases depicting that a vast portion of plant species is yet to be explored which can cause a revolution in the treatment of cancer[9]. Various phytochemicals and their derivatives are present in diverse parts of the plants like seeds, flowers, bark, fruit, leaf, embryo, and rhizomes[43]-[44]. In addition, these phytochemicals and their derivatives possess various pharmacological properties like anti-inflammatory, antimicrobial, antifungal, antihypertension, antiaging, antioxidant, immunomodulator, antimalarial, anticancer etc.

Various plant-derived products like flavonoids, alkaloids, terpenes, vitamins, glycosides, minerals, oils, gums, biomolecules and other metabolites (primary or secondary) have proven their anticancer potential owing to various mechanisms; inhibition of cancer cell activating proteins, enzymes like cyclooxygenase, topoisomerase, CDK2, Cdc2, CDK4 kinase, MMP, MAPK/ERK, signalling pathways, activation of DNA repair mechanism, induction of antioxidant action or stimulation of the formation of protective enzymes (Caspase-3, 7, 8, 9, 10, 12)[45]-[46] (Figure 3).

Various preclinical studies have demonstrated that the combination of phytochemicals with conventional anticancer drugs is more efficacious than phytochemicals individually to treat cancer due to the fact that plant derived compounds have low anticancer efficacy than conventional anticancer drugs.

Various phytochemicals having the potential to improve anticancer activity in codelivery include curcumin, resveratrol, genistein, epigallocatechin gallate, allicin, quercetin, thymoquinone, piperine, naringenin, naringin, emodin, luteolin, β-carotene, anthocyanins, berberine, ursolic acid, withaferin A, sulforaphane, colchicine[47],[13] (Figure 4).

Although phytochemicals have huge potential as anticancer drugs these also suffer from various limitations such as low solubility, poor bioavailability, high dose, narrow therapeutic index, fast absorption by the normal cells, high apparent volume of distribution leading to accumulation of drugs in normal cells, high clearance rate, short elimination half life[13],[48]. However, phytochemicals also have the potential to improve the anticancer property of other chemotherapeutic agents by decreasing their adverse effects[49]-[50]. Hence these days, plant-derived drugs or phytochemicals are used in combination with conventional chemotherapeutic agents for efficacious treatment of cancer with low adverse effects[51] .

5. **Figure 1 also needs to be modified (related to "phytochemicals" and "nanocarrier?"). Information on the occurrence of simple cancers is not required.**

Ans: In figure no.1, our aim was to provide the basics of cancer along with its progression. We have now incorporated your valuable suggestions also in Figure no.1. However, we have provided the information about the phytochemicals and nanocarrier in figure number 6 which states that Various nanocarriers like solid lipid nanoparticles, nanostructured lipid carriers, nanoemulsions, polymeric nanoparticles, polymeric micelles, liposomes, dendrimers, carbon nanotubes, metallic nanoparticles, nanoemulsions have been utilized for codelivery of anticancer drugs owing to their ability to entrap the drugs followed by release on targeted site[74]-[75] (Figure 6). Moreover, they also protect the drug molecules from hazardous environmental factors which can cause gastrointestinal degradation of the drugs[76]. The modification in shape, size, and surface properties of nanocarriers can be performed to elicit maximum efficiency which leads to improved drug efficiency, decreased adverse effects, avoidance of multiple drug resistance, and maximization of drugs in targeted cells[77].

**Figure 1**: Various stages for the progression of cancer along with their treatment approaches

**Figure 6**: Mechanism of various nanocarriers to target the drug at the cancer site

6. **Chapter 5 is good, but it is needed to break up the paragraphs and clarify the content for the potential readers.**

Ans: Thank you for your valuable suggestion. We have break up the Chapter 5 in paragraphs to clarify the content for potential readers.

7. **Check the grammar of the words in Figure 2 again.**

As per your suggestions, we have made some changes in figure 2.

**Figure 2:** Various hindrances associated with conventional anticancer drugs

8. **Overall, I think it will help to understand if I divide the paragraphs and describe them.**

Ans: By keeping in mind your valuable suggestion we have break up the manuscript in paragraphs for the interest of the potential readers.

**9. It would be good to reflect the classification (nanocarriers) in Chapter 6 in Table 2 as well. The contents of Table 2 are good, but the classification is awkward. For example, What does simple nanoparticle (Table 2) mean (not SLN?, NLC?) ?**

Ans: Thank you for valuable suggestions of the reviewer. We have classified all the nanocarriers with specific category the table 2 in chapter 6 (Exosomes, lipid nanoparticles have been classified as polymeric nanoparticles).

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## Round 2

### *Reviewer 1 Report*

Only one additional concern. Could you discuss the progress of clinical trials of listed phytochemicals as monotherapy if no co-delivery system? For example, for curcumin, extracellular vesicle has been used to deliver curcumin (NCT01294072).

*Author Response*

**Reviewer 1**

1. **Could you discuss the progress of clinical trials of listed phytochemicals as monotherapy if no co-delivery system? For example, for curcumin, extracellular vesicle has been used to deliver curcumin (NCT01294072)**

Ans: Till date, no combination of conventional anticancer drug with phytochemicals is available as anticancer treatment but curcumin in monotherapy is in clinical trials in market as anticancer drugs. In NCT01294072, a phase I randomized clinical trial was conducted to study the ability of plant exosomes to deliver curcumin to normal or colon cancer tissues enrolling 35 participants. The recruitemnt status was recruiting. The primary outcome measure of study were to compare the concentration of curcumin in normal tissues and cancerous tissues after 7 days of ingestion and secondary outcome measures were safety and tolerability of curcumin alone as determined by adverse events after 7 days of enrollement[53].

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### *Reviewer 2 Report*

The answers to the previous questions are nice, but the authors made few changes to the text and abstact.

It is recommended that it be published after further revision.

1.Check all abbreviated words in the text. WHO is unexplained and EPR is explained three times.

2.It's not good to start with "therefore" or "however" in the paragraph. Replace them all if possible.

3.Make sure all paragraphs are semantically complete. Overall, the content is too listed.

4. "In a study" appears too many times in the text. It is better to change it to something else in a variety of different expressions.

5. There is an error in the font size in the text.

*Author Response*

**Reviewer 2**

**1.Check all abbreviated words in the text. WHO is unexplained and EPR is explained three times.**

Ans: Thank you for pointing out this. As per your suggestions, we have corrected abbreviations throughout the manuscript.

**2.It's not good to start with "therefore" or "however" in the paragraph. Replace them all if possible.**

**Ans:** Thank you for providing insightful and valuable suggestion. As per your suggestion, we have deleted or replaced the above mentioned words throughout the manuscript.

**3.Make sure all paragraphs are semantically complete. Overall, the content is too listed.**

Ans: As per your suggestion, we have gone through complete manuscript and we made some changes where the paragraphs were not semantically complete.

4. **"In a study" appears too many times in the text. It is better to change it to something else in a variety of different expressions.**

Ans: Thank you for valuable suggestion of the reviewer. As per your suggestions, we have made changes throughout the manuscript.

5. **There is an error in the font size in the text.**

Ans: Thank you for pointing out this point. We have done same font size throughout the manuscript.

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# Local Drug Delivery Strategies towards Wound Healing

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**Kamla Pathak** [2,*] **(mailto:kamlapathak5@gmail.com)** **(https://orcid.org/0000-0001-9074-3752)**

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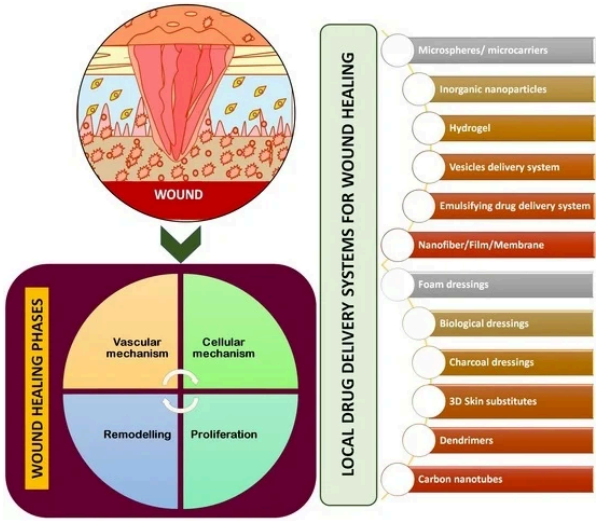
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## Abstract

A particular biological process known as wound healing is connected to the overall phenomena of growth and tissue regeneration. Several cellular and matrix elements work together to restore the integrity of injured tissue. The goal of the present review paper focused on the physiology of wound healing, medications used to treat wound healing, and local drug delivery systems for possible skin wound therapy. The capacity of the skin to heal a wound is the result of a highly intricate process that involves several different processes, such as vascular response, blood coagulation, fibrin network creation, re-epithelialisation, collagen maturation, and connective tissue remodelling. Wound healing may be controlled with topical antiseptics, topical antibiotics, herbal remedies, and cellular initiators. In order to effectively eradicate infections and shorten the healing process, contemporary antimicrobial treatments that include antibiotics or antiseptics must be investigated. A variety of delivery systems were described, including innovative delivery systems, hydrogels, microspheres, gold and silver nanoparticles, vesicles, emulsifying systems, nanofibres, artificial dressings, three-dimensional printed skin replacements, dendrimers and carbon nanotubes. It may be inferred that enhanced local delivery methods might be used to provide wound healing agents for faster healing of skin wounds.

**Keywords: wound (/search?q=wound)**; **physiology of wound healing (/search?q=physiology+of+wound+healing)**; **strategies towards wound healing (/search?q=strategies+towards+wound+healing)**; **local delivery systems (/search?q=local+delivery+systems)**

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Graphical Abstract

## 1. Introduction

One of the most crucial characteristics of simple bacteria to complex multicellular creatures is an undamaged outer coating. The largest organ in the human body, the skin serves a variety of purposes. Skin is susceptible to a range of external variables because of its exposure to the environment, which can lead to various skin injuries and damage. A series of physiological events can heal cuts or injuries because skin has remarkable regenerating abilities. The epidermis of the skin is central to several vital organs, including apocrine glands, eccrine sweat glands, and hair follicles with pilosebaceous units [**1**]. A wound is the result of the “disruption of normal anatomic structure and function,” claims the Wound Healing Society. Depending on how long a wound takes to heal, attention might be given to the acute and chronic kinds. Acute wounds are typically treated effectively with a good possibility of success within a few weeks and are primarily caused by mechanical trauma or surgical procedures [**2**]. The location, size, depth, and type of an acute wound all affect its nature. The chain of events necessary for wound healing can be disrupted by a variety of disease processes, leading to chronic, non-healing wounds that cause the

patient great suffering and need a tremendous number of resources from the medical system. The coagulation cascade, inflammatory pathways, and the cellular components of the immune system are all activated during wound healing, which causes a significant modification of all skin compartments [**3**]. For expediting in vivo wound healing and minimising scar formation, cellular scaffolds containing fibroblasts, keratinocytes, stem/progenitor cells, or reprogrammed cells have shown promising outcomes.

Depending on the type of wound and the patient, several wound treatments are used, but they all often start with cleaning, involve taking antibiotics, and involve choosing the right dressing [**4**]. The dressing should encourage autolytic debridement and be non-toxic, non-allergenic, non-adherent, and non-toxic. For deep wounds or after surgery for patients with implanted medical devices, effective local administration of antibacterial chemicals is crucial. Surface-adherent cells may release growth factors that may then affect the timing and result of the creation of a scar as skin cells move into a fibrin-rich temporary matrix to form a scar. A polymer applied therapeutically to the local site of interest may help such local wound-healing activities [**5**].

When serious cuts are treated with typical wound care techniques, permanent scars are created. As a result, considerable effort has gone into creating alternative therapies that bring back the natural skin's capacity for regeneration. Cell treatment, growth factor delivery, gene delivery, and other techniques have all been utilised to speed up the healing of non-healing wounds. Drugs and genes can have their half-lives extended, their bioavailability increased, their pharmacokinetics optimised, and their dose frequency decreased using drug delivery systems at the nano, micro, and macroscales [**6**]. If just extracellular delivery is necessary, microparticle-mediated distribution would have a more long-lasting therapeutic impact since the release kinetics would be slowed by the reduced surface-to-volume ratio. Protein and nucleic acid treatments, on the other hand, would require nanoparticle-mediated transport in order to reach the intracellular targets. Nanotechnology has a fantastic chance to improve currently used medical therapies, standard care, and wound management [**7**]. It has been discovered that nano drug delivery methods are non-toxic, completely compatible with skin, and favourably generate a helpful moist environment for activating and accelerating the wound healing process.

When comparing different drug delivery methods, tissue-engineered scaffolds are particularly pertinent to wound healing since they can act as a depot for medicines [**8**]. Additionally, they can serve as wound dressings to physically protect the wounds. Therefore, drug-incorporated scaffolds hold great promise for speeding the healing of chronic wounds through a combination of mechanisms. By acting through immune regulation, paracrine actions, and differentiation into epidermal and dermal cells to restore the injured skin, stem cell-based treatments show increasing promise [**9**]. The application of particular stem cells has emerged as a promising strategy to overcome the drawbacks of conventional treatments, offering the potential

to improve the healing of chronic wounds as well as speed up the process of wound healing for acute wounds [**10**]. There are several different antibiotic formulations that can be used topically on wound sites. Medicine delivery devices are particularly crucial because when a drug is given systemically, the poor vasculature in the wound bed can prevent the drug from effectively reaching the healing tissue. Additionally, complicated drug delivery systems that can transport the active ingredients in the right quantity to the right area are needed due to the side effects of some medications, the short half-lives of biological components, and the dynamic nature of the wound environment [**11**].

The physiology of wound healing as well as current advancements in wound healing techniques, with a focus on local medication delivery elements, are critically examined in this review article.

## 2. Physiology of Wound Healing Process

Skin wound healing is an intriguing biological process that has served mammals well throughout evolution. Skin wound healing is a crucial phase for survival that culminates in wound closure because of its essential roles as a physical, chemical, and bacterial barrier. The process of cellular, humoral, and molecular mechanisms involved in skin wound healing is dynamic, tightly regulated, and can take years to complete [**12**]. The epithelialisation of skin wounds depends on the details of the lesion, including its location, depth, size, microbial contamination, patient-related medical problems, genetics, and epigenetics. Following a skin injury, the exposed sub-endothelium, collagen, and tissue factor will stimulate platelet aggregation, which in turn causes degranulation and releases chemotactic factors (chemokines) and growth factors to form the clot [**12**]. By following all of the aforementioned steps, successful haemostasis will be achieved.

A skin wound can heal completely through regeneration or repair. Skin repair shows an unspecific kind of healing in which the lesion heals by fibrosis and scar formation, in contrast to regeneration, which depicts the specific substitution of the tissue, such as the superficial epidermis, mucosa, or foetal skin. Unfortunately, the latter is the primary mode of adult skin wound healing [**13**]. The pathophysiology of chronic wounds is still poorly understood; however, it is known that they remain in the inflammation stage of the healing process rather than progressing further. Critical obstacles to the physiologic healing of chronic wounds include impaired vascularisation and the resulting hypoxia, the inability to move on to the healing phase, extended and exacerbated inflammation, and the incapacity of immune cells to manage bacterial infection. Normal wound healing can be hampered by prolonged wound-healing phases or overly aggressive reactions of the organism to the damage [**14**]. The majority of chronic wounds heal through fibrosis, which produces an excessive quantity of connective tissue rather

than regeneration. Additionally, persistent inflammation is followed by fibrosis, and fibrosis-healing wounds have been discovered to have higher levels of pro-inflammatory mediators (such as TGF-β) (**Figure 1**). Unnecessary fibroblast proliferation, neovascularisation, and increased collagen and fibronectin synthesis are all results of poorly controlled growth factor activity. Additionally, a wound contracts too much and for too long, causing fibrotic scar tissue to grow. Keloids and hypertrophic scars are two different types of pathological scars that can result from an injury. In this regard, there is active current study on the change from the inflammatory to the proliferative stage of wound repair. Three to five phases that overlap in both time and location can be artificially created to represent the various stages of wound healing [**12**,**13**,**14**,**15**,**16**].

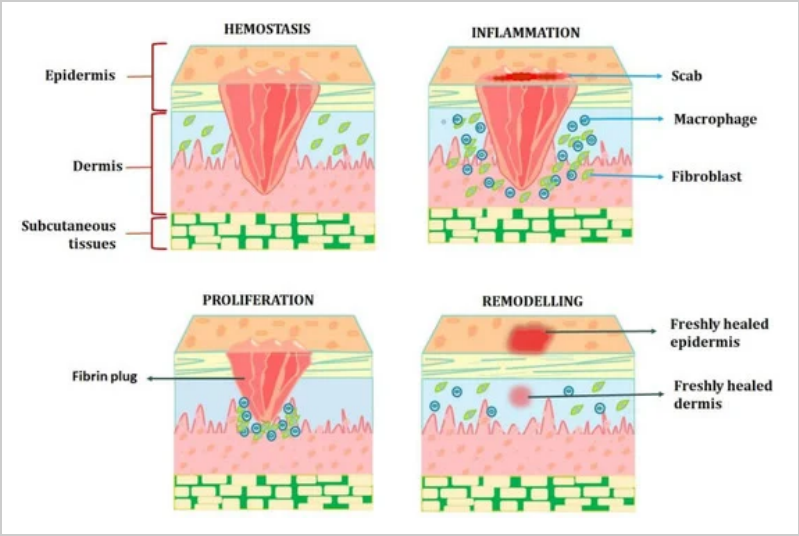



**Figure 1.** Physiology of wound healing. Haemostasis: The immediate response to a surgical injury is the vasoconstriction of blood vessels at the point of injury. Inflammatory process: brings nutrients to the area of surgery, removes debris and bacteria, and provides stimuli for wound repair. Proliferation: involves processes of angiogenesis, granulation tissue production, collagen deposition, and epithelialisation. Remodelling: Type 1 collagen replaces the type 3 collagen found in granulation tissue, and a scar forms.

### *2.1. Haemostasis and Coagulation: Vascular Mechanism*

The thrombogenic sub-endothelium is initially exposed to platelets by haemorrhage into the wound. When the skin is wounded, bleeding typically occurs to help remove microorganisms and/or antigens from the wound. The main goal of the

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vascular mechanism is to stop exsanguination in order to maintain the integrity of the circulatory system and ensure important organs' abilities to function unharmed despite the injury. The long-term provision of a matrix for the invasive cells that are required in the later stages of healing is the second goal. Bleeding causes haemostasis to be activated, which occurs by exudate components such as clotting factors [**17**]. Vasoactive chemicals such as serotonin and catecholamines work through particular endothelium receptors to constrict nearby blood vessels. Leukocytes, red blood cells, and plasma proteins can enter the body by way of smaller arteries when they are triggered to vasodilate. A local perfusion failure with subsequent oxygen deprivation, increased glycolysis, and pH alterations is explained by the life-saving vasoconstriction with clot formation. Following vasoconstriction, there is a vasodilation during which thrombocytes infiltrate the temporary wound matrix [**18**]. Hyperaemia, a localised redness, and wound oedema are additional signs of vasodilation. Platelets are essential to this stage, as well as the overall healing process, because, in addition to establishing early haemostasis, they also release a number of cytokines, hormones, and chemokines that initiate the subsequent stages of healing. In order to prevent further blood loss, the coagulation cascade is activated alongside haemostatic processes through intrinsic and extrinsic routes, causing platelet aggregation and clot formation. The presence of fibrinogen in the exudate triggers the clotting mechanism, which causes the exudates (blood devoid of cells and platelets) to coagulate (**Figure 2**). This, along with the construction of a fibrin network, results in a clot in the wound, which stops bleeding [**19**]. The fibrin, fibronectin, vitronectin, and thrombospondin molecules found in the blood clot serve as the provisional matrix, a scaffold for the migration of leukocytes, keratinocytes, fibroblasts, and endothelial cells as well as a source of growth factors. Additionally, this stage is where the inflammatory process starts. This stage is occasionally referred to as the “lag phase” because the organism must coordinate the recruitment of numerous cells and components for the healing process while the wound lacks mechanical strength [**18**,**19**,**20**].

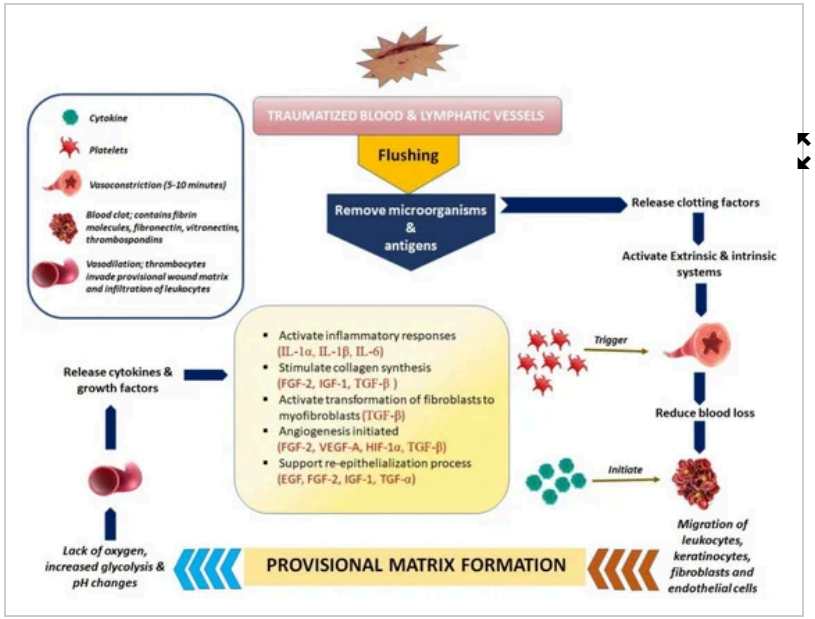



**Figure 2.** Vascular mechanism for Haemostasis and coagulation. This mechanism is regulated by a dynamic equilibrium between endothelial cells, thrombocytes, coagulation, and fibrinolysis, which also influences the amount of fibrin deposited at the wound site and affects how quickly the reparative processes proceed.

### *2.2. Inflammation: Cellular Mechanism*

The inflammatory phase starts practically immediately after haemostasis and lasts for around 3 days, often starting as soon as a few minutes after damage and lasting up to 24 h. Through the production of histamine and serotonin, the release of protein-rich exudate into the wound produces vasodilation, allowing phagocytes to enter the wound and devour dead cells (necrotic tissue). It starts the complement cascade and sets off molecular processes that allow neutrophils, whose primary job it is to fight infection, to infiltrate the wound site. To remove bacteria, foreign objects, and injured tissue, the neutrophils must first perform the vital process of phagocytosis [**21**]. Within the first 24 h, many neutrophils arrive on the scene as the initial leukocytes. Macrophages quickly follow neutrophils because they are drawn to the consequences of neutrophil death. In the wound, phagocytic cells such as macrophages and other lymphocytes start to sweep away debris and microorganisms.

About 48 h after the injury, these macrophages infiltrate and remain there until the inflammatory phase is over. Long considered the main cell in the healing of wounds, macrophages appear to coordinate the most crucial stages of healing

(**Figure 3**) [**22**]. Recent studies have looked at their role in both poor healing and scarring, despite the fact that they are essential to normal recovery. Re-epithelialisation, granulation tissue development, angiogenesis, wound cytokine production, and wound contracture are intricate processes involving macrophages. The succeeding procedures depend on phagocytotic activity because acute wounds with a bacterial imbalance are unable to heal. Inflammation is brought on as circulating monocytes enter the tissue and quickly mature into adult macrophages. By activating type-1 macrophages (M1), phagocytosis eliminates pathogens, foreign objects, necrotic neutrophils, and wound dermis from the diseased area. They generate a number of cytokines and proinflammatory mediators. Mastocytes are sensitive to tissue damage and play a crucial role in the healing process by secreting a number of cytokines that promote the recruitment of white blood cells [**17**,**18**,**19**,**20**,**21**,**22**]. T cells enter the wound site and control a variety of processes. Monocytes, cytokines, macrophages, corneocytes, big granular lymphocytes, T-lymphocytes, basophils, granulocytes, and vascular endothelial cells are all involved in wound regeneration. IL-1, TNF-α, IL-6, VPF, TGF- β, and IGF-1 are among the cytokines produced by monocytes, which develop into macrophages. Along with corneocytes, fibroblasts, granulocytes, and vascular endothelial cells, neutrophils, such as T lymphocytes and basophils, are important makers of TNF-α, IL-10, and other chemokines. VEGF, IGF-1, and TGF- β are all produced by macrophages [**12**,**13**,**14**]. As a result, each of the cells mentioned above participates in the intricate process of tissue repair. Subsequent repair mechanisms of an adult depend on cell and tissue movements that are caused by growth factor and cytokine signals, which are provided by the inflammatory response to injury. Epithelial cells and fibroblasts travel to the injured location during the migration phase to replace lost and damaged tissue. These cells quickly spread over the wound beneath the dried scab (clot), regenerating from the borders and thickening the epithelium [**23**].

**Figure 3.** Inflammatory phase following a cutaneous incision. Inflammatory cell invasion: Early inflammatory phase activates the complement cascade and initiates molecular events while in the late phase, macrophages appear in the wound and continue the process of phagocytosis.

### *2.3. Proliferation*

Because the proliferative stage of wound healing is highly metabolic with an increased demand for oxygen and nutrients, the restoration of blood flow is essential. For phagocytes undergoing a respiratory burst to effectively combat pathogens, the presence of oxygen in cutaneous wounds is also essential.

### 2.3.1. Epithelialisation

The multiplication and inflow of keratinocytes close to the wound's leading edge indicate epithelialisation. Re-epithelialisation begins during the proliferative phase of wound healing, roughly 16–24 h after injury, and continues through the second and third phases. It is characterised by fibroblast migration and the deposit of a recently created extracellular matrix, which takes the place of the temporary fibrin and fibronectin network [**18**]. Capillary budding and the synthesis of the extracellular matrix are also involved in the repair phase to fill in the gaps left by the debridement of the wound. Hair follicle and apocrine gland bulbs contain stem cells that start to develop into keratinocytes, repopulate the stratum basale, and move over the edge of the wound. They connect close to the inner edge of the wound once they come into contact with the mesenchyme of the extracellular matrix (ECM), and they start to lay down a new basement membrane. Keratinocytes are crucial for maintaining the barrier as well as for its repair after injury through a process called epithelialisation. Undifferentiated keratinocytes convert into differentiated non-dividing cells during differentiation as they move upward to eventually give rise to the cornified envelope [**24**]. The process of differentiation is mediated by three main mitogen-activated protein kinase (MAPK) pathways, which are activated by a variety of stimuli, including calcium influx, epidermal growth factor (EGF), and TNF-α. K6, K16, and K17 keratins are upregulated in migrating keratinocytes, which is thought to augment the viscoelastic characteristics of moving cells. In addition to producing paracrine and autocrine signals that are directed at surrounding keratinocytes, activated keratinocytes also alert fibroblasts, endothelial cells, melanocytes, and lymphocytes. In order to coordinate the activity of neighbouring cell types in the repair of damaged tissue, these responses are crucial [**25**].

### 2.3.2. Angiogenesis

In response to tissue injury, the complicated mechanism of angiogenesis is heavily controlled by signals from the ECM and serum. Activated macrophages, the epidermis, and soft tissue wounds can all produce angiogenesis. Gelatinase A is released by endothelial cells exposed to thrombin, and it aids in the local disintegration of the basement membrane, an essential first step in angiogenesis. Many soluble factors, most notably VEGF-A, positively influence the initiation of angiogenesis. Due to its powerful angiogenesis and vasopermeability activity, VEGF, a growth factor belonging to the PDGF family, was initially called the vasopermeability factor [**22**]. The VEGF family in mammals consists of five members (VEGF-A, -B, -C, and -D and placenta growth factor). In the wound, thrombin increases cellular receptors for VEGF. Due to a hypoxic gradient between injured and healthy tissue, expression of the HIF-1 gene causes the synthesis of VEGF. Nitric oxide generation by endothelial cells is also influenced by hypoxia [**25**]. To increase local blood flow, nitric oxide encourages angiogenesis and vasodilation. The most

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important proangiogenic factor in wound healing is VEGF-A, which is produced in response to hypoxia. A powerful proangiogenic mediator, VEGF-A also raises vascular permeability, which adds to wound oedema. Other factors, such as cardiac ankyrin repeat protein, as well as VEGF-A, FGF-2, PDGF, TGF-β family members, and other factors also encourage wound angiogenesis. Numerous highly technical depletion investigations on skin have shown that macrophages are a significant contributor to overall proangiogenic stimulation. Thus, it appears that in the healing wound, inflammation and the subsequent angiogenic response are related [**26**].
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#### 2.3.3. Granulation Tissue Formation

Granulation tissue normally grows from the wound's base and can cover any size wound. Chronic wound formation can be caused by any mistakes in the granulation tissue creation process. Fibroblasts, freshly sprouting blood vessels, and immature collagen make up granulation tissue (collagen type III) [**25**]. In this stage, some fibroblasts will also start differentiating into myofibroblasts, which can contract to close wound edges that are protruding from the body. TGF-β and PDGF, which are generated by inflammatory cells and platelets, entice fibroblasts and myofibroblasts from the surrounding tissue to move into the wound [**27**,**28**]. Through the creation of granulation tissue brought on by hypoxia, increased lactate, and different growth factors, healing through secondary intention is accomplished. Epithelisation over this granulation is a necessary step in healing by secondary intention, followed by substantial remodelling [**29**]. Any medicine that prevents the growth of new blood vessels may hinder the healing of wounds. In addition to the collagen matrix, fibrinogen, fibronectin, and hyaluronic acid, macrophages, proliferating fibroblasts, and vascularised stroma also make up the acute granulation tissue that takes the place of the fibrin-based provisional matrix. The blood vessels become less dense as collagen builds up, and the granulation tissue gradually reaches maturity to form a scar [**30**].

### *2.4. Remodelling Phase*

Through cell apoptosis, the production of granulation tissue is stopped. Cellular connective tissue is generated during tissue maturation or remodelling, and the newly formed epithelium is strengthened. From a few months to around two years, cellular granular tissue transforms into an acellular mass. Fibroblasts and macrophages are important players in remodelling. Several growth factors, including TGF-β, PDGF, and FGF, which are stimulated during tissue injury and repair, control remodelling. Although the function of growth factors in the development of scars is not entirely known, TGF-β is assumed to be significant [**26**]. By boosting the development of tissue inhibitors of metalloproteinase and causing an increase in collagen deposition, this factor is known to decrease pro-collagenase production and enzyme activity. The collagen that was put down

during proliferation is eventually replaced by a more stable interwoven type III collagen during remodelling as the water content of the wound decreases. In order to maintain a precise balance between synthesis and degradation and promote normal healing, regulatory mechanisms carefully govern the remodelling of an acute wound. Concurrent with the development of the granulation tissue, the extracellular matrix begins to be synthesised during the proliferative and remodelling phases. The proliferative phase's collagen III is now being replaced by the more robust collagen I. Later, the myofibroblasts generate wound contractions through various collagen attachments and aid in reducing the surface area of the scar [**31**,**32**].

## 3. Wound Healing Strategies

### *3.1. Cellular Activity Initiators*

DNA synthesis is promoted in fibroblast cells by secretions from healthy wounds. Conversely, the same fibroblasts are inhibited by the secretions from long-lasting, nonhealing wounds, such as leg ulcers. Interestingly, heating the fluid contents of a chronic wound denatures them, removing the inhibitory impact and restoring fibroblast growth. As before, fibroblasts from chronic wounds have the worst response to growth factors than fibroblasts from acute wounds, suggesting that the fibroblasts in chronic wounds are also harmed. The most promising biomarkers are proteases and cytokines. Traditional medicines such as honey, curcumin, and tannin have been studied using modern pharmaceutical practices to learn how they affect cellular activity. One would anticipate that cytokine release, which represents neutrophil and macrophage activity, would increase in an effort to trigger a fibroblast response if fibroblasts stop responding. The pro-inflammatory cytokines IL-1 and TNF-α were found in higher concentrations in non-healing wounds than in healing wounds. When the healing starts, the levels significantly decrease. An electromechanical coupling bio-nanogenerator made of extremely discrete piezoelectric fibres was created by Tong et al. [**33**]. By using the inherent force of the cell, it can produce a surface piezopotential up to millivolts, providing in situ electrical stimulation for the living cells. Additionally, the three dimensional structure of bionanogenerator encourages growth of ECM. Bio-nanogenerators successfully support cell viability and development as a result, but more crucially, they maintain the cell's unique functional expression.

Several methods were used to modulate macrophages, including blocking IL-1 or TNF-α, inhibiting the inflammasome pharmacologically, neutralising MCP-1, and chelating iron with desferrioxamine. Sulphated hyaluronic acid is internalised by macrophages after being identified by CD44 and the scavenger receptors CD36 and LOX-1. Most notably, it prevents the phosphorylation of the transcription factors including pNFkB, pSTAT1, and IRF5 that are involved in M1-like activation states

and the production of pro-inflammatory genes. Sulphated hyaluronic acid regulates macrophage activation in vivo. Inhibiting the secretion of growth factors by macrophages, blunting the immune system's response to presented antigens, blocking the conversion of membrane phospholipids to arachidonic acid, and reducing vascular permeability are a few of the ways that steroids modify the inflammatory process at various stages of the cascade of wound healing.

By altering fibroblast activity and proliferation, anti-fibrotic medications such as mitomycin C and 5-FU stop the formation of scars. By disrupting pyrimidine metabolism, the anti-proliferative activity of 5-FU is mediated. By preventing the production of thymidine nucleotides, it prevents DNA synthesis, leading to cell death. It has long-lasting effects on Tenon's fibroblasts and can effectively limit fibroblast development [**34**]. By reducing to an alkylating agent, mitomycin C is activated and subsequently works by cross-linking DNA. Mitomycin C can impede not just DNA replication but also mitosis and protein synthesis. Hypermongone C, a polycyclic polyprenylated acylphloroglucinol, was shown by Ehsan et al. [**35**] to have the ability to speed up wound closure by simultaneously boosting fibroblast proliferation and migration, encouraging angiogenesis, and inhibiting pro-inflammatory cytokines. This substance comes from the Hypericum plant family, which has long been used to cure wounds. There are now more opportunities for the combination of therapeutic strategies in multifunctional ECM-based wound dressings thanks to ECM-based materials that have already been investigated for the delivery of antimicrobials and sustained release of angiogenic and pro-fibrotic growth factors in wound healing. Proteomic and microbiome analyses, gene sequencing, high-resolution imaging, and single-cell laser capture are some of the new technologies that may offer comprehensive information that helps define macrophage subtypes with distinct activation profiles in physiologically healing wounds and recognise their dysregulation in chronic wounds. Improvements in collagen production and angiogenesis have been reported using microspheres carrying FGF-10 [**36**].

### *3.2. Collagen Synthesis Activators*

In addition to providing resident cells with structural support, collagens, which are found in the dermis as fibrillar proteins, also control resident and inflammatory cell function. Since collagen plays a crucial role in the healing of wounds, chemicals that alter the molecular processes that cause collagen synthesis have been recognised as effective wound-healing medications. In in vitro and in physiological settings, the collagenase from the bacteria *Clostridium histolyticum* hydrolyses triple-helical collagen utilising synthetic peptides as substrates. The anti-collagenase activity of phytoconstituents and crude extracts from natural resources has received extensive study. Numerous phytoconstituents found in plants, including polyphenols with collagenase inhibitory activity, such as flavonoids, terpenoids, glycosides, vitamin E, vitamin C, phenolic acids, and tannins, are

abundant. Reduced collagen production and stability, slower re-epithelialisation, and an elevated susceptibility to infection have all been linked to vitamin A insufficiency [**37**].

*Ascorbic acid* (vitamin C), is crucial for the manufacture of collagen. The collagen that is produced in scurvy is unhydroxylated, relatively unstable, and prone to collagenolysis. A lack of vitamin C causes fibroblasts to create unstable collagen, which offers a flimsy foundation for repair. Although it is generally known that animals with vitamin C deficiencies take longer to repair wounds, it is unclear whether oral vitamin C supplements speed up the healing process. A lack of vitamin K impairs the generation of the clotting factors (factors II, VII, IX, and X), which leads to bleeding disorders, the formation of haematomas, and consequent negative effects on wound healing [**38**]. In order to transport oxygen, iron is needed. The immune system and other mineral systems depend on substances such as copper and zinc. Lack of zinc causes the production of granulation tissue to be disrupted. *Aloe vera* is a natural substance that is still frequently used and acknowledged in domestic and professional settings as a tool for treating wounds. Aloe vera is primarily recognised for its ability to lessen pain in burn wounds, but it also helps wounds produce more collagen.

Collagenase and dexpanthenol-containing ointment formulations have been used to speed up re-epithelialisation, reduce fibroblast proliferation, and rebuild the ECM. Due to their advantageous effects, topical preparations of growth factors have recently been investigated in wound healing. Growth factors have a low bioavailability, which limits their use because they are quickly removed from the wound site. Emerging strategies that topically apply growth factors are nanoparticle-encapsulated and have improved stability and bioavailability to the wound area aim to address this limitation. Rats with parenchymal lung lesions experienced better wound healing and an increase in the presence of immature collagen after intraperitoneal glutamine treatment [**39**]. Dietary glutamine supplementation increased the collagen density in colonic anastomoses in rats, indicating that fibroblasts can synthesise enough glycine for collagen production, whereas they need a source of extracellular glutamine. Glutamine availability can also control collagen mRNA expression in fibroblasts [**40**].

### *3.3. Angiogenesis Activators*

By acting as a chemoattractant for neutrophils, macrophages, and fibroblasts, TGF-β promotes the development of granulation tissue. As a result, TGF-β is a crucial regulator of angiogenesis during the healing of wounds because it controls cell division, migration, capillary tube formation, and ECM deposition. Through the production of particular proteins, gene augmentation brings about the return of normal cellular function. By delivering DNA or mRNA into the target cells, one can enhance genes. Exciting new choices for treating chronic wounds will be made possible in the following ten years by wound

dressings that contain sustained nucleic acid delivery systems for promoting angiogenesis and therapy that targets the underlying morbidities. Reactive oxygen species (ROS)-scavenging hydrogel and oxygen-release microspheres were combined to create a sustained oxygenation system by Ya et al. [**41**]. In diabetic wounds, the continuous release of oxygen increased keratinocyte and dermal fibroblast survival and migration, encouraged the development of angiogenic growth factors and angiogenesis, and reduced the expression of pro-inflammatory cytokines. The pace of wound closure was greatly accelerated by these effects. With its interactions with a number of immune and non-immune cells, C1q is a well-known starter of the complement classical route and induces complement activation-independent activities. One of the probable targets of C1q, which binds to receptors found on cell surfaces and promotes inflammation, are endothelial cells. C1q has a special and hitherto unknown role in promoting angiogenesis through the globular heads. The ability of C1q to stimulate the growth of new blood vessels in both in vitro and in vivo models of wound healing provided evidence for its angiogenic action [**42**]. In order to promote the healing of wounds, Jin et al. created temperature-responsive nanobelt fibres that contain vitamin E. A correct matrix elasticity that encourages mesenchymal stem cell adhesion and angiogenesis was given by the cross-linked collagen sheets created by the nanoparticles [**43**]. Additionally, the scaffold encouraged endothelial cells to form tubes. The therapeutic potential of nanoparticle formulation results in the stimulation of angiogenesis. The flexibility of collagen sheets was improved by praseodymium-cobaltite nanoparticle cross-linking for the pro-angiogenic and stem cell differentiation ability [**44**].

### *3.4. Cytokine and Growth Factor Activators*

Small, secreted proteins called cytokines influence not only the activity of immune cells but also that of other cells. Interleukins, lymphokines, and several related signalling molecules, such as TNF-α, interferons, and others, are among them. Through the activation of cell surface TGF-β serine/threonine type I and type II receptors and the activation of a Smad3-dependent signal, active TGF-β1 induces the fast chemotaxis of neutrophils and monocytes to the wound site. Leukocytes and fibroblasts that have expressed TGF- β1 are then stimulated to produce additional cytokines, such as TNF-α, IL-1β, and PDGF, as well as chemokines, which are all part of a cytokine cascade. Such factors serve to maintain the inflammatory cell response by influencing neutrophil and monocyte recruitment and activation. TGF-β and other cytokines that activate their corresponding cell surface receptors cause intracellular signalling pathways to be activated, which, in turn, causes target cell populations to respond phenotypically and functionally. NF-κB, early-growth response 1 (EGR1), Smads, and MAPK are some of the upstream signalling cascades involved in acute tissue injury. These cascades activate many cognate target genes, including adhesion molecules, coagulation factors, cytokines, and growth factors. The platform upon which circulating leukocyte-

expressing counter-adhesion molecules (integrins, selectins, and Ig superfamily members) tether allows them to sense the microenvironment and react to chemotactic signals at the site of tissue injury. This is accomplished by cytokine-induced enhancement of adhesion molecules (VCAM-1, ELAM-1, and ICAM-1) on the endothelium. In response to various chemotactic cues, transmigration from within to outside the artery wall is made possible by interactions between adhesion molecules on blood leukocytes and endothelium. Numerous chemokines are generated in addition to the chemotactic action of TGF-β1 for neutrophils and monocytes to attract leukocytes to the site of tissue injury. Depending on where the cysteine residues are located, several families of related molecules serve as representations of chemokines [**45**].

Growth factors such as PDGF, TGF-β, and EGF are secreted when platelets degranulate and release alpha granules. PDGF plays a crucial role in luring neutrophils to the wound site to eliminate contaminated germs, coupled with proinflammatory cytokines such as IL-1. A number of pro-inflammatory cytokines (IL-1 and IL-6) and growth factors (FGF, EGF, TGF-β, and PDGF) are released by macrophages to support the development of granulation tissue. One of the first substances to be created in response to skin lesions is a substance known as a proinflammatory cytokine, which controls immune cell actions during epithelialisation. TNF-α, IL-1, IL-6, and IL17 are the main proinflammatory cytokines that play a role in the inflammation phase of wound healing. They also play a role in the epithelialisation phase by promoting cell proliferation and differentiation and mobilising local stem/progenitor cells. Cytokine modulators are a new class of medicinal drugs that prevent fibrogenesis. Scarring and fibrosis of the skin are frequently the results of excessive fibrogenesis [**46**]. As a different strategy to prevent fibrosis, the modulatory effects of natural compounds such as terpenes and honey should be taken into consideration. Mitomycin P modulators such as buckwheat and acacia honey should be taken into account as substances reducing scarring and encouraging re-epithelisation. Terpenoids are frequently present in essential oils and serve as cytokine suppressors, increasing the production of IL-10 and the anti-inflammatory cytokines TNF- and IL-1 [**47**].

### *3.5. Antimicrobials*

There is a lot of debate about the application of topical antibiotics to wounds. Topical antimicrobial agents are described as substances that can eliminate, suppress, or lessen the number of bacteria. These substances include disinfectants, antiseptics, and antibiotics. Topical antimicrobial medicines are essential to topical burn care because they are used to prevent and control infection. The ideal topical preventive antimicrobial agent would be able to enter necrotic tissue without being absorbed by the body, have a broad spectrum of activity, a lengthy duration of action, have low toxicity, and have several other qualities [**48**].

A renewed interest in silver-based medications is a result of concerns about bacterial resistance. For thousands of years, silver has been utilised in medicine for its antibacterial properties. A good environment for wound healing can be created by using topical antimicrobials that do not impede epithelial outgrowth and deliver a high concentration of active components to devitalised, devascularised, and, perhaps, necrotic wounds. Topical antibacterial use may reduce the requirement for extensive debridement and subsequent grafting as well as wound deepening. Although microorganisms are present in every wound, the majority do not become infected and heal properly. In these circumstances, the immune system of the host and the bioburden of the wound are in equilibrium [**49**]. NF-κB is nuclear translocated as a result of toll-like receptor (TLR) stimulation through intracellular signalling from adapter proteins, which, in conjunction with mitogen-activated protein kinases, triggers the transcription of a variety of inflammatory cytokines, chemokines, antimicrobial peptides, and costimulatory factors. According to wound specialists, there is a threshold over which antimicrobial intervention is necessary when bacteria loads are more than or equal to 104 CFU/g. Silver compounds are among the antibacterial agents used in burn treatment. In cases when surgery is either not possible or would not be the first option right away, such as in cases of facial burns, silver sulphadiazine is frequently utilised and acts on burn eschar to restrict the area of non-viable tissue [**50**,**51**,**52**,**53**,**54**,**55**]. Since silver is a natural broad-spectrum antibiotic, there has not been any bacterial resistance to its treatments yet. There are numerous types of silver, including silver oxide, silver nitrate, silver sulphate, silver salt, silver zeolite, silver sulfadiazine, and silver nanoparticles. When silver cations come into touch with liquid, they are freed from their carrier dressings. Depending on the dressing employed, there are significant differences in the pace, duration, and peak level of silver released. Once discharged, silver kills germs in a variety of ways. The healing of both acute wounds and chronic wounds is currently aided by various forms of silver. Antiseptic and antibiotic dressings are the two primary categories into which antimicrobial dressings can be divided.

Due to their good efficacy and tolerability among the various antimicrobial agents available, iodophor-based formulations such as povidone iodine have remained well-liked after decades of usage for antisepsis and wound healing applications. Povidone iodine has been reported as having a wide range of activity, the capacity to penetrate biofilms, a lack of related resistance, anti-inflammatory qualities, low cytotoxicity, and good tolerability. In clinical practice, no adverse effects on wound healing have been noted. Another antimicrobial agent that penetrates burned tissue is cerium nitrate. It has a wide range of activity against Gram-positive and Gram-negative bacteria, as well as fungal species, and is highly effective when used in conjunction with silver sulphadiazine [**56**]. Povidone iodine is fully hazardous to keratinocytes and fibroblasts at concentrations greater than 0.004 and 0.05%, respectively [**57**,**58**,**59**,**60**,**61**,**62**,**63**,**64**,**65**,**66**,**67**,**68**,**69**,**70**,**71**,**72**,**73**,**74**]. According to in vitro testing, cadexomer iodine is not harmful to fibroblasts at doses up to 0.45%. At doses between 0.2 and 0.001%, chlorhexidine

also exhibits dose-dependent toxicity to fibroblasts. Antiseptics are primarily used to avoid infection, reinfection, and probable disruption of wound healing. Antiseptic therapy also has the secondary purpose of promoting wound healing by stimulating cell growth and regeneration. These effects have been shown for polyhexamethylene biguanide, in addition to pure microbicidal action (polyhexanide). Antiseptics also have additional beneficial benefits, such as wound cleaning, which can aid in debridement. Effective antiseptics for local wounds include polyhexanide and octenidine dihydrochloride. Nitrofuran and natrium fusidate are other antibacterial substances (**Table 1**) [**48**,**49**,**50**,**51**,**52**,**53**,**54**,**55**,**56**,**57**,**58**,**59**,**60**,**61**,**62**,**63**,**64**,**65**,**66**,**67**,**68**,**69**,**70**,**71**,**72**,**73**,**74**,**75**,**76**,**77**,**78**,**79**,**80**,**81**,**82**,**83**,**84**,**85**,**86**].

**Table 1.** Commonly used antimicrobial agents with target species.

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The lipid–protein complex produced from damaged skin that is responsible for the severe immunosuppression linked to significant cutaneous burns is believed to be bound and denatured by cerium. Additionally, cerium nitrate hardens burn eschar, which is supposed to inhibit bacterial entry and maintain a moist wound. A broad-spectrum antibacterial agent, silver is efficient against yeast, bacteria, fungus, and viruses. When taken at the right concentration, it has also been demonstrated to be effective against vancomycin-resistant enterococci and Methicillin-resistant *Staphylococcus aureus* (MRSA) [**81**,**82**,**83**,**84**,**85**,**86**]. Additionally, silver is believed to lessen wound irritation and speed up recovery. The local wound environment affects the amount of silver required to have a bacteriostatic or bacteriocidal impact. It has shown to be effective against pathogens on the surface, but it might not have an impact on bacteria that have travelled a long way into the wound bed. So, when colonisation or critical colonisation is detected, silver may be utilised to assist in lowering the bacterial count in mild wound infections.

### *3.6. Stem Cell-Based Therapy*

A promising new method in the area of regenerative medicine is stem cell-based therapy. The ability of stem cells to self-renew and specialise into distinct cell types is essential for physiologic tissue renewal and regeneration after injury, and is of

great interest to biologists. Adult mesenchymal stem cells, embryonic stem cells, and, the more recently studied, induced pluripotent stem cells are the main sources of stem cells that are used for skin regeneration and wound healing among the several types of stem cells [**57**]. In essence, keratinocytes are produced from stem cells found in the skin's basal layer, which differentiate for three to six weeks before becoming corneocytes, which in turn create the stratum corneum layer. Keratin, a protein that plays a significant structural role in the stratum corneum, is one of the many proteins that keratinocytes generate. Along with proteins, the stratum corneum's complex lipid and cell membranes act as a significant barrier against bacteria and dehydration. The migration of fully developed cuboidal basal keratinocytes with large nuclei, phospholipid membranes, and organelles starts from the basal layer after roughly every 28 days [**80**,**81**,**82**,**83**,**84**,**85**,**86**,**87**].

A greater build-up of keratin and lipids develops throughout this turnover process and proceeds through terminal differentiation to form a stratum corneum. The dermo-epidermal junction, a basement membrane that separates the epidermal and dermal layers, is where the hemidesmosomes, which serve as cell adhesion molecules, are attached. Keratinocytes from the basal layer, ECM components, basal lamina, filaments, and anchoring fibrils make up the intricate dermo-epidermal junction structure. In order to reduce the possibility of the epidermis separating from the dermis layer, the dermo-epidermal junction must be restored during the wound healing process. The stem cell-based therapy for chronic wound healing makes use of a variety of processes, including growth factor interactions and activities, inflammation control, and immune process stimulation, for speeding vascularisation and re-epithelialisation. The ability of stem cell-based wound therapy to produce pro-regenerative cytokines and growth factors to encourage skin regeneration during the treatment of chronic wounds is largely responsible for its therapeutic potential [**88**,**89**].

### *3.7. Herbal Alternatives Acting as Activators for Wound Healing Factors*

Wound healing may benefit greatly from a variety of plants or chemicals derived from plants that contain high concentrations of antioxidants and have anti-inflammatory, immunomodulatory, and antibacterial characteristics. Antioxidants help tissues recover from injury and can speed up wound healing. The antioxidant activity of flavonoids, anthraquinones, and naphthoquinones is strong. Shikonin, alkanin, lawsone, emodin, epigallocatechin-3-gallate, ellagic acid, and a few herbal extracts have strong antioxidant effects by scavenging ROS, preventing lipid peroxidation, and boosting intracellular antioxidant enzyme activities such as superoxide dismutase, catalase, and glutathione peroxidase [**3**,**8**]. Additionally, herbal medication encourages angiogenesis, fibroblast cell growth, and the production of temporary ECM.

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Herbal extracts and other natural products' immunomodulatory and anti-inflammatory properties hasten the healing of wounds. It is true that plants, and the chemical substances derived from them, aid in healing and treatment. Some herbal remedies stimulate the expression of VEGF and TGF-β, both of which are crucial in stimulating angiogenesis, granulation tissue development, and the deposition of collagen fibres. Other herbal medicines used in wound dressings act as inhibitors of the expression of the proteins TNF-α, IL-1, and inducible nitric oxide synthase, resulting in the induction of antioxidant and anti-inflammatory properties during different stages of the wound healing process. In the healing of cutaneous wounds, curcumin promotes the proliferation of fibroblasts, the development of granulation tissue, and the deposition of collagen [**14**,**15**]. Cinnamon bark has some therapeutic characteristics, including anti-inflammatory, anti-diabetes, anti-ulcer, anti-microbial, and hypoglycaemic effects. It can also help with diabetic and infected wounds. In addition to the above-mentioned qualities, cinnamon is known to contain considerable amounts of polyphenols, which may improve an animal's ability to absorb glucose. Cinnamaldehyde, 2-hydroxycinnamaldehyde, and quercetin are anti-inflammatory properties of cinnamon components that can speed up wound healing. *Aloe vera* gel's antioxidant qualities, which are attributable to certain components including indoles and alkaloids, have positive benefits on the healing of wounds [**90**]. Burns, ulcers, and surgical wounds remain as first-line conditions for *Aloe vera* treatment. Numerous organic bioactive substances, such as pyrocatechol, saponins, acemannan, anthraquinones, glycosides, oleic acid, phytol, and simple and complex water-soluble polysaccharides, are found in *Aloe vera*. *Aloe vera* has a variety of wound-healing mechanisms, most of which are attributable to raising the level of lysyl oxidase and the turnover rate of the collagen in the tissue. IL-1, IL-1, IL-6, TNF-α, PGE2, and nitrous oxide are only a few of the proinflammatory mRNAs that are transcribed when acemannan, a primary mucopolysaccharide from *Aloe vera*, is consumed. Reactive oxygen species and endogenous mitogen inhibitors are bound and captured by mesoglycan molecules, which facilitates phagocytosis.

Glycans prolong the activity of released cytokines, growth factors, and other bioactives. Through the action of cyclin D1 and AKT/mTOR signal pathways, topically administered acemannan has been shown to drastically shorten the time to wound closure in a rat wound healing model. It is well known that *Anethum graveolens* has antibacterial, anti-diabetic, and anti-inflammatory qualities that can speed up wound healing. Major constituents of dill essential oil include cis-carvone, limonene, phellandrene, and anethofuran. Burns, blisters, herpes, cuts, wounds, skin infections, and insect bites are just a few of the skin conditions that eucalyptus oil is traditionally used to treat [**91**,**92**,**93**]. *Securigerasecuridaca* is well known for its antibacterial properties, and helps infected wounds heal faster [**94**]. Antioxidant, anti-inflammatory, antidiabetic, cancer-preventive, antibacterial, antiviral, antimalarial, hypotensive, immunostimulatory, and hepatoprotective properties are all present in

*Andrographis paniculata* extracts. In one study, it was found that treatment with a 10% aqueous leaf extract of *Andrographis paniculata* considerably improved the rate of wound closure in rats [**95**]. The polysaccharides diosgenin, yamogenin, gitogenin, tigogenin, and neotigogens are found in the seeds of *Trigonella foenum-graecum*. Saponins have steroidal actions that can reduce bodily inflammation. Fenugreek also contains mucilage, volatile oils, flavonoids, and amino acid alkaloids, which are bioactive components. 4-Hydroxyisoleucine is the other substance in fenugreek that is active. Fenugreek is said to release an anti-inflammatory chemical into the area of a cut, which reduces inflammation. Fenugreek's antibacterial qualities may also enhance its anti-inflammatory effects. According to a study, the antibacterial characteristics of flavonoids and triterpenoids may help the wound healing process. Antioxidant properties of fenugreek are thought to hasten wound healing. The topical use of the fenugreek seed significantly increased the kinetics of wound contraction and epithelialisation [**96**].

In vivo studies have demonstrated that *Arctium lappa* root extract dramatically improves dermal ECM metabolism, affects glycosaminoglycan turnover, and minimises the appearance of wrinkles in human skin. *Arctium lappa* is also known to influence the Wnt/-catenin signalling pathway, which is recognised to be a significant regulator of wound healing, by regulating cell adhesion and gene expression in canine dermal fibroblasts. In diabetic rats, *Astragalus propinquus* and *Rehmanniaglutinosa* improve angiogenesis and reduce tissue oxidative stress to promote diabetic wound healing and post-ischaemic neovascularisation. In human skin fibroblasts, *Astragalus propinquus* and *Rehmanniaglutinosa* stimulated enhanced ECM deposition by activating the TGF-β signalling pathway. TNF-α and TGF-β1 levels were seen to be higher two days after the damage and to decrease as the wound healed. IL-10, on the other hand, was shown to be raised after 14 days, concurrent with wound healing [**97**]. Topical therapy with ethanolic *Ampelopsis japonica* increased re-epithelisation, granulation tissue development, vascularisation, and collagen deposition when compared to wounds treated with Vaseline or silver sulfadiazine.

Pharmacological benefits of *Angelica sinensis* include immunological modulator, anti-inflammatory, and anticancer properties. In human skin fibroblasts, extracts from Angelica sinensis have been demonstrated to promote cell proliferation, collagen secretion, and cell mobility while also activating an antiapoptotic mechanism. Additionally, extracts have been demonstrated to promote calcium fluxes and glycolysis, enhancing cell viability during tissue healing. Numerous studies have found conflicting results on *Angelica sinensis'* impact on the development of new blood vessels, raising questions about the plant's role in angiogenesis [**98**]. By changing the expression of connective tissue growth factor (CTGF) and smooth muscle actin in vivo, extracts from the *Calendula officinalis* flower promote the formation of granulation tissue in excisional wounds of BALB/c mice. *Blumea balsamifera*, also known as kakoranda in Ayurveda, is used to cure rheumatism, coughs, fevers, and pains. Eczema, dermatitis, skin damage, bruising, beriberi, lumbago, menorrhagia, rheumatism, and skin damage are all

treated using leaf extracts that are administered topically [**99**]. It has been discovered that homoisoflavonoids extracted from *Caesalpinia sappan* exhibit anti-inflammatory and antiallergic properties as well as the ability to block viral neuraminidase activity. The main catechin, (-)-epigallocatechin-3-gallate (EGCG), promotes keratinocyte growth and differentiation. By altering TGF-signalling, lowering MMP-1 and MMP-2 expression, and reducing the synthesis of type I collagen in human dermal fibroblasts, EGCG inhibits TGF- receptors. These characteristics suggested that EGCG may have anti-scarring capabilities [**100**].

*Entada phaseoloides* are high in saponins and tannins and are used topically to treat skin lesions as well as analgesic, bacteriocide, haemostatic, and anticancer agents. In diabetic cutaneous wounds, vitamin E controlled inflammation and oxidative stress. Additionally, vitamin E enhanced the anti-oxidative enzymes superoxide dismutase (SOD), glutathione peroxidase (GPX), and catalase (CAT) that are in charge of purging ROS and oxidised macromolecules from damaged tissues. By encouraging the growth of new blood vessels as well as re-epithelialisation, matrix deposition, and collagen synthesis, vitamin E had positive impacts on the wound healing process' later stages (the proliferation and remodelling phases) [**101**]. Vasodilatation, blood lipid regulation, reduced inflammation; antioxidant, anti-cancer, anti-bacterial, anti-allergic, anti-ageing, and immunomodulatory potential are all benefits of *Panax ginseng* [**102**].

## 4. Localised Delivery Systems for Wound Healing

### *4.1. Microspheres/Microcarriers*

A sort of injectable scaffold is a microsphere, often known as a microcarrier. Microspheres offer enough room for cell development and have good surface area-to-volume ratios. To further improve the transport of cells and bioactive compounds, microspheres with functional architectures (such as hollow or core-shell) can be easily customised and manufactured. As a result, functional microspheres have received a lot of attention recently as a new kind of injectable scaffold. Microspheres are typically referred to as spheres with a diameter between 1 and 1000 m. The diameter of most cells when they adhere and spread on a biomaterial is greater than 20 μm; hence, small-sized microspheres (<20 μm in diameter) are not suited as cellular carriers. Microspheres should therefore be between 20 and 200 μm in size when used as an injectable biomaterial for tissue engineering [**103**]. The development and uses of functional microspheres, including macroporous microspheres, nanofibrous microspheres, hollow microspheres, core–shell structured microspheres, and surface-modified functional microspheres, are covered after a brief introduction to the biomaterials and techniques for microsphere fabrication. Li and Wang explained the

perspectives and directions for functional microspheres as injectable cell carriers, which are offered as a final step in the advancement of tissue regeneration [**104**].

Li et al. provide an explanation for the developments in functional microspheres, including the kinds of biomaterials used to make microspheres, the manufacturing processes for functional microspheres, and the uses of functional microspheres for the regeneration of bone, cartilage, the dentin–pulp complex, neural tissue, cardiac tissue, and skin. The use of microspheres has substantially increased as a result of the addition of additional structures and functions [**105**]. The core–shell configuration, for instance, can be easily used to combine cells in a microsphere with a regulated growth factor supply. Within a microsphere, there are numerous areas for cell migration and proliferation due to the hollow structure and macropores on the surface. Additionally, by incorporating nanofibrous architecture into microspheres, an ECM-like microenvironment is created that can direct tissue regeneration. This replicates the structure of natural ECM. Before using functional microspheres from a bench to a patient's bedside, however, there is still considerable work to be undertaken.

The following description highlights some of the major obstacles to the creation of functioning microspheres [**91**,**92**,**93**,**94**,**95**,**96**,**97**]. In order to include biomimetic elements in functional microspheres, newer methods must first be developed. Phase separation is currently the only efficient way to make nanofibrous microspheres. While electrospinning and electrospray are used to create nanofibrous microparticles, their sizes and geometries are not well regulated. The traditional layer-by-layer self-assembly technique has trouble producing spheres smaller than a micrometre. Although one of the most efficient ways to create functional microspheres is using microfluidics, it is still difficult to create nanofibrous microspheres with this technology. More bio-inspired functional microspheres will be developed as a result of new fabrication methods that use modern microsphere fabrication techniques [**103**]. The exact control of bioactive chemical release from microspheres is also required. Currently, the majority of microsphere systems release bioactive molecules over a period of several days to a week, which is insufficient for the regeneration of many tissues. Additionally, there is a significant initial burst release from microspheres, and limiting the burst release is essential to enhancing therapeutic efficacy. The first burst release from functional microspheres is predicted to be tuned and reduced using methods and procedures including novel chemical and physical interaction factors in addition to traditional production parameters, such as polymer concentration and cross-linking time. The third one concerns the mechanical capabilities of microspheres [**104**].

The majority of microspheres are made from polymeric materials and typically have a porous structure; hence, their compressive moduli are quite low. Even though the mechanical strength is increased by adding inorganic elements such as hyaluronic acid, the microspheres still cannot be employed in load-bearing situations. In order to broaden the use of functional

microspheres, research is being conducted to improve the mechanical properties of microspheres. Fourth, more evidence is required to support microspheres' in vivo stability. To avoid diffusion of the microspheres to nearby faulty areas, microspheres are typically chemically cross-linked [**105**,**106**].

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### *4.2. Inorganic Nanoparticles*

Nanomaterials have received a lot of recent attention because of their improved efficacy and broad-spectrum antibacterial potential. Numerous metallic and metal oxide nanoparticles, such as Ag, Fe, Cu, and Au, as well as $TiO_2$, ZnO, and $Fe_3O_4$, are being thoroughly researched for the treatment of infectious disorders. Considering that both of their counterparts are typical of low molecular weight, the two most popular systems of metal nanoparticles (NPs), gold (AuNPs) and silver (AgNPs) provide excellent methods for delivering pharmaceuticals. These nanoparticles have advantages over commonly used antibiotics because of their distinctive features, including size, shape, surface charge, dispersion, and chemical composition. Additionally, these synthetic antibiotics frequently only work against a certain type of bacterium or bacterial family, rendering them useless against a diverse range of bacterial species [**107**]. Currently, antibiotic efficiency has decreased mostly as a result of uncontrolled, excessive dosage, and prolonged use, which has favoured the establishment of multi-drug-resistant bacterial strains or "superbugs" such as MRSA-3. Nanomaterials have received a lot of recent attention because of their improved efficacy and broad-spectrum antibacterial potential.

Additional benefits of these materials include targeted drug delivery, solubility, improved cellular internalisation, tissue/cell selectivity, compatibility with tissue/tumour imaging, minimal adverse effects, etc. Due to their effectiveness in combating bacteria, silver nanoparticles have received the most attention among all those studied. However, little is known about the methods by which these nanoparticles destroy pathogens. It has been suggested that $Ag^+$ ion release occurs from nanoparticles. However, the low stability and extreme cytotoxicity of the majority of silver nanoparticle (AgNP) forms limit their applicability in mammalian cells.

AgNPs must be engineered with various compositions to improve their properties and make them suitable for therapeutic application in order to overcome their current constraints. If these nanoparticles pass the required tests by regulatory agencies for better antibacterial efficacy and minimum cytotoxicity for patients, they may prove to be effective antibiotic alternatives or may be used in conjunction with antibiotics [**106**,**107**,**108**]. The antibacterial activity of metallic nanoparticles has been increased by a number of methods, including encasing silver nanoparticles in micelles, covering silver nanoparticles in gold, and capping gold nanoparticles with 5-amindole or sodium borohydride N-heterocyclic molecules.

A bimetallic nanoparticle with silver and gold was recently developed. Complex carbohydrates on the caps of these bimetallic nanoparticles improve their stability and other characteristics. These bimetallic NPs can be used for in vivo antimicrobial activities since they have considerably better antibacterial activities and do not harm mammalian cells. The use of silver to improve wound healing dates back to ancient times when it was utilised as an ion. Unlike silver ions ($Ag^+$) or other forms of silver, which are used as nanoparticles, silver metal (Ag) has no known medical applications. They can impede the healing process since many bacteria, viruses, fungi, and even yeast is cytotoxic to them. This ion was used as part of a wound dressing that contained silver ions specifically to treat severe wounds [**109**]. In general, silver has numerous beneficial qualities, including broad-spectrum antibacterial activities. Silver-based lotions and other ointments are also available, and silver nanoparticle products can be used in a variety of therapeutic ways to help accelerate wound regeneration. The use of silver as a common bandage has been linked to decreased inflammation foci and scarring, possibly preventing bacterial development, and boosting the healing process, and possibly enhancing remodelling in the wound area, according to multivariate retrospective analyses. Therefore, using nanocomposites that are submerged in silver molecules improves the healing process by directly expressing collagen and certain growth factors that result in re-epithelialisation, neovascularisation, and the deposition of collagen fibres. Additionally, silver nanoparticles can cause the fibroblast to differentiate into myofibroblast, which is in charge of contracting the wound and quickening the healing process, and in a similar way, they can cause keratinocytes to be stimulated, proliferate, and move to the necessary area. For better wound healing, silver nanoparticles encourage keratinocyte migration from the edge into the core of the lesion. According to certain researchers, antimicrobial peptide–AgNP composite has been examined for its ability to speed up the remodelling process without having any negative effects on the dermal tissues. Resonance scattering dark-field microscopy makes use of gold nanoparticles to detect microbial cells and their byproducts, bio-image tumour cells, identify receptors on their surface, and analyse endocytosis [**110**].

Due to their chemical characteristics, optical stability, and simplicity of surface modification, gold nanoparticles (AuNPs) have been researched for medicinal applications such as wound healing. Before using gold nanoparticles for wound healing, they must fuse or have their surfaces modified with other biomolecules. For instance, the effectiveness of AuNPs to promote healing is increased by the addition of polysaccharide peptides. The application of gold nanoparticles to skin wounds boosted angiopoietin, VEGF, and collagen expression while decreasing mitomycin P and TGF-β1 levels [**111**]. It demonstrated decreased bacterial load and aided in recovery. Due to reduced blood circulation, systemically administered antibiotics may have trouble reaching injured skin tissue, rendering them ineffective for lowering bacterial numbers in granulation wounds.

Recently, there has been a lot of fascinating study on the antibacterial properties of AuNPs, which makes them appropriate for possible co-use with antibiotics. Particularly in the 18 wt% composite group, the substance accelerated wound closure by increasing angiogenesis and fibroblast proliferation without inducing cell damage. According to a recent ex vivo permeation study, AuNPs can be effective in the treatment of burns as well since they can speed up the healing process and prevent microbial colonisation while being transdermally active [**112**].

### *4.3. Hydrogel*

Insoluble hydrophilic materials known as hydrogels are created using synthetic polymers such as poly (methacrylates) and polyvinyl pyrrolidone. Complex hydrophilic organic cross-linked polymers called hydrogels have a base that is 80–90% water. These hydrogels can provide water to the wound site and aid in keeping it moist, which promotes quicker wound healing. These are created into contact lenses, drug delivery systems, wound dressings, electrodes, and sensors. These gels can be found as fixed flexible sheets or free-flowing amorphous gels. They have a limited capacity for fluid absorption through swelling, but they can also contribute moisture to a dry wound, aiding in autolytic debridement and maintaining a moist, thermally insulated wound environment [**113**].

Additionally, they have been demonstrated to increase granulation and epithelialisation, lower wound bed temperature, and have a relaxing and cooling effect. They have been shown to be a less efficient bacterial barrier than occlusive dressings and are permeable to gas and water. These dressings are primarily used to moisten dry wound beds and to soften and remove slough and necrotic wound debris. Due to their high-water concentration, they are unable to absorb substantial drainage; they absorb very slowly and are consequently useless on bleeding wounds; and they typically require a secondary dressing. They can be applied to a range of wounds, including vascular ulcers, pressure ulcers, and partial and full-thickness wounds [**114**]. Maceration is a potential problem since the skin around open wounds must be shielded from excessive moisture.

Hydrogels can be used in conjunction with topical drugs or antibacterial agents, which is one of their advantages. Infected wounds should not be treated with hydrogels in their fixed state. Hydrogels must be coated with additional dressings and left on for up to three days. They transfer oxygen and moisture vapour, but the type of secondary dressing employed affects how permeable they are to bacteria and fluids. Until an equilibrium condition is attained, these systems may swell in water and keep their original shape. The process of hydration, which is related to the presence of chemical groups such as -OH, -COOH, -$CONH_2$, and -CONH-, as well as the existence of capillary regions and variations in osmotic pressure, is one of the interactions that contribute to the water sorption by hydrogels [**115**]. These are hydrophilic polymer networks that can absorb 10–20% of

their dry weight in water as well as thousands of times that amount. These can dissolve and deteriorate or they can be chemically durable. When the polymer networks are bound together by molecular entanglements and/or secondary forces such as ionic and H-bonding, they are referred to as “reversible” or “physical” gels. When hydrogels have covalently bonded networks, they are referred to as “permanent” or “chemical” gels [**116**].

High-intensity radiation, freeze–thaw, or chemical processes can all be used to create hydrogels. Radiation, such as gamma rays, electron beams, X-rays, or ultraviolet light, is thought to be the most suited way for the creation of hydrogels since it allows for simple processing control and eliminates the need for potentially dangerous initiators or cross-linkers. Additionally, sterilisation and possible formation are both possible with irradiation. However, the mechanical strength of the hydrogels produced using this approach is subpar. Today, hydrogels are made using a freeze–thaw process to give them good strength and stability without the need for additional cross-linkers and initiators. The hydrogels’ limited swelling and thermal stability, as well as their opaque appearance, are the principal drawbacks of freeze–thawing. The application of hydrogel appears to considerably stimulate wound healing as compared to the standard gauze therapy. In order to create hydrogel wound dressings, a variety of natural and synthetic polymers with good biocompatibility are used [**117**].

There are several different types of hydrogels, including interpenetrating polymeric hydrogels, copolymer hydrogels, multipolymer hydrogels, and homopolymer hydrogels. In contrast to copolymer hydrogels, which are created by the cross-linking of two co-monomer units, one of which must be hydrophilic, homopolymer hydrogels are cross-linked networks of a single type of hydrophilic monomer unit. The cross-linking of more than three monomers results in the formation of multipolymer hydrogels. Finally, the swelling of a first network in a monomer and the reaction of the latter to generate a second intermeshing network structure results in interpenetrating polymeric hydrogels. It has been established that combining a natural polymer with a synthetic polymer appears to be a successful way to create materials with the necessary mechanical and thermal properties. It is also a quick process for producing the right forms, such as films, sponges, and hydrogels, to make a variety of biomedical devices.

For instance, chronic non-healing wounds are known to have an environment that is highly alkaline, whereas the healing process is more effective in an acidic environment. Therefore, manufactured dermal patches that can measure the pH of the wound continuously are essential for guiding point-of-care treatments and monitoring the healing process of chronic wounds. Since they are porous and permeable to oxygen and gas, hydrogels offer a lot of promise for use in biomedicine. They may be suggested as materials for both burn skin treatment and wound dressings. The hydrogel membrane was created based on a polyvinyl alcohol hydrogel, which may absorb wound exudates and release water, medications, or biomolecules (such as

growth factors or antibiotics), creating the ideal environment for the healing of wounds. The epidermal sensor can also measure the ambient temperature, which allows it to deliver useful biological data regarding the state of the wound [**118**,**119**,**120**].

### *4.4. Vesicles Delivery System*

Vesicular systems, which can be further divided into liposomes, ultra-deformable liposomes, and ethosomes, are composed of amphiphilic molecules because they have polar or hydrophilic regions and non-polar or lipophilic regions. It has been demonstrated that vesicular systems, including liposomes, niosomes, transferosomes, penetration enhancer-containing vesicles, and ethosomes, can improve the therapeutic activity of medications used to treat wounds. They can lengthen the shelf life of hydrophilic and hydrophobic medications and lessen major side effects including skin irritation, and act as a depot for controlled drug release. They can also improve the penetration of such medications into the skin. The two types of vesicular systems are hard vesicles, such as liposomes and niosomes, and flexible or ultra-flexible vesicles, such as transferosomes.

According to reports, rigid vesicles are ineffective for transdermal drug delivery because they stay on the stratum corneum's outer layer and do not thoroughly penetrate the skin. After topical administration, liposomes can cause a variety of reactions. The majority of efforts have been concentrated on the topical treatments' antibacterial action, which has fallen short due to the rising rate of antibiotic resistance. They can inhibit systemic absorption, maximise side effects, and provide a localising impact as well as tailored distribution to skin appendages. They can also improve drug deposition within the skin at the site of action. Additionally, these vesicles were crucial in the healing of wounds [**121**]. Antibiotics entrapped in liposomes exhibit reduced toxicity and more target specificity along with increased efficacy in treatment of bacterial infections and thus improve its pharmacokinetics and pharmacodynamics. Increased action against external pathogens that are resistant, as well as increased activity against intracellular pathogens, is also an attractive feature. Due to their occlusive action on the stratum corneum, lipid nanoparticles may be more appropriate in burn wounds and chronic wounds since they can prevent transepidermal water loss and maintain the lesion moisture. Additionally, compared to vesicular systems, nanostructured lipid carriers are offered as superior nano-delivery methods. They have great stability, low toxicity, high drug-loading capacity, and sustained drug release, which helps speed up wound healing and cuts down the number of drugs administered [**122**].

#### 4.4.1. Conventional Liposomes in Wound Healing

Because each pathophysiology differs, distinct skin wounds may require different treatments. According to the extent of the burn, acute burn wounds not only cause harm to the skin's structures but also to all of the body's systems because of the leakage of plasma into interstitial spaces. Additionally, the compromised skin barrier makes people more vulnerable to bacterial

infections. In order to maintain skin functionality, it is crucial to prevent infections and promote re-epithelialisation while treating burn wounds. The majority of efforts have been concentrated on the topical treatments' antibacterial action, which has fallen short due to the rising rate of antibiotic resistance. In order to combat infections and promote skin regeneration in burn wounds, a variety of nanosized lipid-based delivery systems, including liposomes, transferosomes, ethosomes, and lipid nanoparticles, have been investigated. The results are encouraging [**122**,**123**].

New treatments for chronic wounds have been made possible by advancements in vesicular drug delivery systems, which have decreased the cost, toxicity, and number of applications while enhancing the half-life and bioavailability of the medications. The lowered membrane permeability of madecassoside, a highly powerful substance used to heal wounds, was likewise outperformed by liposome encapsulation. A formulation with a high entrapment efficiency, excellent long-term stability, and small particle size was discovered. Furthermore, double-emulsion liposomes enhance transdermal penetration and wound healing, despite the fact that liposomes are non-toxic, biodegradable, and skin-compatible. Curcumin and quercetin have also been included in the liposomes. Polyphenols quercetin and curcumin have antioxidant and anti-inflammatory properties that are helpful for wound healing [**124**].

#### 4.4.2. Ultra-Deformable Liposomes or Transferosomes in Wound Healing

As a result of the creation of new vesicular systems called ultra-deformable liposomes, elastic vesicles, or transferosomes, conventional liposomes are currently used less frequently as transdermal delivery systems. Vesicles' suppleness allows them to deform and enter skin pores that are much smaller than their diameters as intact vesicles. Ultra-deformable liposomes enter undamaged skin and penetrate deeply, allowing the systemic circulation to absorb them. Here, a transdermal hydration gradient allows the ultra-deformable liposomes to pass through the intact stratum corneum and enter the epidermis. This is a result of the vesicles' high degree of deformability, which is brought on by the presence of surfactants, also referred to as "edge activator" molecules. With the ability to solubilise and fluidise epidermal lipids, edge activators have a significant impact on the exceptional deformability of transferosomes and increase their permeability capacity. Recently, consideration has been given for their capacity to traverse the stratum corneum among vesicular transferosomes. Transferosomes can transmit low bioavailability medications via the skin, according to numerous studies. Due to their deformability and ability to resist dry environments, transferosomes can pass to deeper skin layers undamaged. Transferosomes are therefore typically used for transdermal medication delivery in addition to their potential for topical distribution due to their capacity to penetrate deeply through epidermal layers and reach systemic circulation without the risk of vesicle rupture [**121**,**123**].

#### 4.4.3. Ethosomes and Phytosomes in Wound Healing

Drugs that are both extremely hydrophobic and highly hydrophilic now have easier access to the deep skin layers thanks to ethosomes. Depending on how much ethanol is present, the ethosomes can range in size from 103 to 200 nm. The second generation of liposomes can be introduced as ethosomes. As a result, the vesicular systems' storage stability is a major challenge. However, ethosomes have more stability than regular liposomes. Several studies have looked into the utility of ethosomes in the treatment of wounds and have found that ethosomes transfer active ingredients to the skin more effectively than liposomes or conventional formulations. Recent research has shown that natural ingredients and antibacterial agents are more effective when they are encapsulated while treating burn wounds. In a different study, the ability of ethosomes loaded with silver sulfadiazine, a topical antibiotic regarded as the gold standard in burn wounds, to speed up the healing process and decrease bacterial infections in second-degree burns, was examined in vivo and in vitro. High entrapment efficiency is offered by phytosomes, which can be employed to distribute phytoconstituents topically for wound healing. The preparation was discovered to be risk-free and to have considerable antioxidant and wound-healing properties [**123**,**124**,**125**].

### *4.5. Emulsifying Drug Delivery System*

The oral distribution of such medications is frequently linked to inadequate bioavailability, considerable intra- and inter-subject variability, and a lack of dose proportionality. Approximately 40% of novel drug candidates have poor water solubility. The use of surfactants, lipids, permeation enhancers, micronisation, salt formation, cyclodextrins, nanoparticles, and solid dispersions are just a few of the formulation strategies that have been used to tackle these issues. Recently, lipid-based formulations have received a lot of attention, with a focus on self-emulsifying drug delivery systems to increase the oral bioavailability of lipophilic medications. The fact that self-emulsifying drug delivery systems offer a significant interfacial area for the partitioning of the medication between oil and water is another benefit they have over straightforward oily solutions. Therefore, these systems may provide an improvement in the pace and amount of absorption as well as more consistent plasma concentration profiles for lipophilic medicines with dissolution-limited oral absorption [**126**].

By combining water and the non-ionic surfactant Tween 20 (Polysorbate 20), Ghosh et al. created a cinnamon oil microemulsion. Oil and surfactant were consumed in a 1:4 ratio. The microemulsion was discovered to be kinetically stable and generated with droplets that were around 5.79 nm in diameter. Ponto et al. studied that a microemulsion with antibacterial properties promotes wound healing in Wistar rats. In order to increase the solubility and bioavailability of hydrophobic/lipophilic medicines such as curcumin, self-emulsifying drug delivery systems are crucial substitute vehicles. Self-emulsifying drug

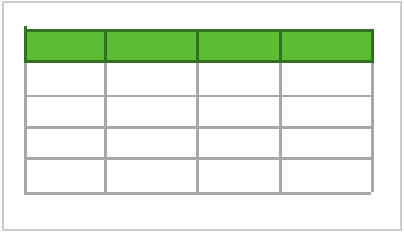
delivery systems are physically stable isotropic mixes of oil/lipids, surfactants, and co-surfactants/co-solvents that have a great deal of potential as therapeutic drug delivery systems. To achieve the required therapeutic objectives, the self-emulsifying drug delivery systems formulations represent the hydrophobic drug in a solubilised state (nanoglobules) in the target location [**127**]. Through a number of methods, including drug solubilisation, droplet size reduction, improved membrane permeability, and protection of pharmaceuticals from chemical and enzymatic degradation, the self-emulsifying drug delivery systems formulations can increase drug bioavailability.

Different self-emulsifying drug delivery systems formulations were created and tested with an eye toward skin applications, including self-emulsifying drug delivery systems for the topical delivery of mangosteen peel and self-emulsifying drug delivery systems for the transdermal drug delivery of curcumin, *Opuntia ficusindica* fixed oil, *Piper cubeba* essential oil, and *Opuntia ficusindica* fixed oil (*Garcinia Mangostana* L.). The absorption of self-emulsifying drug delivery systems by the fibroblasts was found to be linearly dependent and dose-dependent. When curcumin is synthesised into nanocarriers, which have the least amount of cytotoxicity when compared to free drug solution, the cellular uptake of curcumin is facilitated [**125**,**126**,**127**,**128**].

### *4.6. Nanofiber/Film/Membrane*

One of the most significant areas of science and technology in the twenty-first century that can be likened to the industrial revolution is nanotechnology. Soon, nanotechnology will have a substantial impact on the global economy and industry, as well on as the technology used by humans and their way of life. In the past, different materials such as animal fat, plant fibres, honey, etc., have been used to cover wounds (**Table 2**). Polymers have been employed in several research studies to make films for use as wound dressings. With two external dimensions that are identical in size at the nanoscale (about 100 nm) and a third dimension that is noticeably larger, nanofibres are one of the most fascinating classes of nanomaterials. Depending on the medication’s solubility in the polymer solution, a polymer solution (polymer + particular solvent) is first created, after which a predetermined proportion of the drug is added, resulting in either a homogenous solution or a suspension [**126**,**127**,**128**,**129**,**130**,**131**]. This combination is electrospun to create nanofibres that contain a solid polymer–drug complex.

**Table 2.** Localised delivery systems of several drugs.





A wide range of polymers can be used to create nanofibres. For dressing nanofibres, there are only three types of polymers now available: natural polymers, synthetic polymers, and mixed polymers. Natural polymers are appropriate for use in biomedical applications due to their wide range of benefits, including biocompatibility, non-toxicity, biodegradability, antibacterial properties, and desirable mechanical structure. In the procedure, the solvent evaporates. On the other hand, nanofibres are made of a polymeric base, which makes up most of the fibre's composition, and a bioactive molecule (such as a protein, hormone, or medication), or another type of polymer, but in a lesser amount than the base polymer. Currently, the three primary techniques for producing nanofibres are electrospinning, the phase-separation method, and the self-assembly method. The method that produces nanofibres most frequently is electrospinning. Depending on the electrospinning technique employed, various types of nanofibres can be produced. Today, the commercialisation of electrospinning equipment is advancing quickly. The most popular electrospinning methods include bubble electrospinning, melt electrospinning, coaxial electrospinning, self-bundling electrospinning, and nano-spider electrospinning [**132**,**133**,**134**,**135**,**136**,**137**,**138**,**139**,**140**,**141**,**142**,**143**,**144**]. Fibre electrospinning processes can be used to create polymer nanofibres (50–1000 nm) (wet or hot melt electro-spinning). Numerous excellent characteristics of nanofibres include their substantial surface area, the potential for surface functionalisation, tunable porosity, a broad range of material options, and outstanding mechanical performance. The advantageous characteristics of electrospun nanofibres, such as mechanical stability, high porosity, high surface area to volume ratio, and ability to exchange water, oxygen, and nutrients, encourage good cell attachment, differentiation, and proliferation. They enable the monitoring of infection and healing markers due to their capacity to mimic the structure and operation of ECM [**145**]. The nanofibres are excellent candidates for a variety of biomedical applications, such as tissue-engineered scaffolds (such as skin, cartilage, bone, and blood vessels), dressings for wound healing, biomedical devices, biosensors, and drug delivery systems, because of their exceptional capabilities. Electrospun nanofibre mats offer a native extracellular matrix-like structure with high interconnected porosity (60–90%), great absorbencies, and a water absorbance capacity of 18–21% more than films made of the same polymers [**146**]. These characteristics, along with balanced moisture and gas permeability, create an environment that is suitable for preventing exogenous infection, cell migration and proliferation,

haemostasis, exudate absorption, and cell respiration in wounds. Electrospun nanofibres can control the proliferation, migration, differentiation, and synthesis of native extracellular matrix in skin cells.

Tissue engineering and wound healing are two of the most important and intriguing biomedical uses of nanofibres. Nanofibres have been utilised in the treatment of diabetic ulcers and wounds to aid in wound healing, haemostasis, skin regeneration, and wound dressing. Nanofibre keeps the wound surface moist while healing because it can hold more moisture in its structure. As a result, the nanofibres cannot adhere to the surface of the wound. Additionally, the porous nanofibre network makes it simpler for oxygen to diffuse into the wound area. To remove toxins from the blood of individuals with kidney failure, wearable blood purification systems may integrate the nanofibre membrane. Nanofibre scaffolds hold great promise for wound healing. These scaffolds are used in the treatment of diabetic ulcers, skin rejuvenation, wound dressings to encourage healing, and haemostasis [**147**,**148**]. Nanofibres keep the wound area moist while it heals because of their capacity to hold more moisture within their structures. As a result, the scaffold cannot adhere to the damaged surface. Furthermore, oxygen may easily diffuse to the location of the wound thanks to the porous networks. Nanofibres have the power to regulate a range of skin cell responses, including proliferative, migratory, differentiating, and extracellular matrix accumulation. Their microstructure ideally complements the ECM structure, which encourages cellular proliferation, adhesion, and growth. While creating a larger surface area than bulk materials, nanofibre arrangements have increased porosity, which is advantageous for cell activities.

The polymers used to create scaffolds for wound dressing include collagen, poly-vinyl pyrrolidone, polyacrylic acid, polyvinyl alcohol, gelatin, chitosan, silk fibroin, polyesters, and poly-urethane [**149**]. The goal of a wound dressing is to quickly achieve haemostasis, and it should also have strong antibacterial properties to guard against bacterial infections from the environment. The ability of electrospinning to construct nanofibrous membranes for wound dressings that can provide a moist environment surrounding the wound region to facilitate healing has drawn a great deal of interest. In order to create composite nanofibre membranes that carry a reservoir of biogenic AgNPs for use as a wound dressing, Bardania et al. used *T. polium* extract as a reducing agent. This method of “green synthesis”, which does not use external stabilisers or reducing agents, produced AgNPs quickly, cheaply, and effectively [**76**,**82**,**109**].

### *4.7. Foam Dressings*

Foam dressings are permeable to both gases and water vapour and have a polyurethane foundation. The outer layer’s hydrophobic qualities shield it from liquids while allowing gaseous exchange and the passage of water vapour. Silicone-based

MDPI (/)

rubber foam, or silicone, conforms to the shape of wounds. Depending on the thickness of the wound, foam can absorb varied amounts of wound drainage. There are foam dressings that are both adhesive and non-adhesive. Lower leg ulcers, mild to heavily exuding wounds, and granulating wounds can all benefit from foam dressings. They offer both thermal insulation and excellent absorption thanks to their hydrophilic characteristics [**153**]. These incredibly adaptable dressings should be used on moderate-to-heavy exudative wounds, partial- and full-thickness wounds that are granulating, or slough-coated donor sites, ostomy sites, mild burns, and diabetic ulcers. Due to their capacity to cause wounds to become even drier, they are not advised in dry or eschar-covered wounds and vascular ulcers. Due to their high absorbency and moisture vapour permeability, they are typically utilised as main dressings for absorption, and supplementary dressings are not necessary. The disadvantage of foam dressings is that they need to be changed frequently and are not appropriate for low exudating wounds, dry wounds, or dry scars since they need exudates to heal. They can stay in place for up to 4 to 7 days, but once they become saturated with exudates, they need to be changed. When removed, they are non-traumatic due to their makeup. They can also be applied to infected wounds if they are changed daily [**39**]. Numerous papers have examined various foam dressing forms, mostly because of their propensity for liquid and/or permeability to moisture vapour. These characteristics may make some foam more suitable for treating weakly exudative wounds as opposed to lesions that drain excessively [**154**]. The primary limitation of this kind of dressing is that it requires a second dressing, such as an elastic bandage or a film, to adhere to the wound. Foam dressings are used for deep wounds that have produced a lot of exudates as well as for long-term wounds such as venous ulcers. They may also be applied under compression bandages [**149**,**153**].

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### *4.8. Biological Dressings*

In order to restore the wound healing process and incorporate active biological agents to assist the wound healing process, advanced biological therapies are currently emerging in ischaemic wound therapies. The use of active biological agents, such as plant-derived active biomolecules with antioxidant, antibacterial, or anti-inflammatory properties, may be used in biological wound-healing therapies, which aim to aid the restoration of the body’s natural repair mechanisms. Biological dressings stop contamination, heat loss, protein and electrolyte loss, and evaporative water loss [**15**,**22**]. Bioactive wound dressings can be created using naturally occurring biomaterials with endogenous activity or materials that release bioactive chemicals. Chitin, chitosan, hydrocolloids, alginate, and derivatives of organic biopolymers are a few examples of these biomaterials. Biological dressings made from animal collagen are known as collagen dressings. The fibroblast-produced protein collagen plays a part in each step of wound healing. The extracellular matrix is primarily made up of collagen, which gives it

strength [**29**]. This category includes dressings made from collagen sourced from bovine, porcine, or avian sources. These products are all intended to hasten the healing process. Protease activity is decreased by both collagen and oxidised regenerated cellulose (ORC), which is usually coupled with collagen. Proteases have a variety of roles in the healing of wounds, albeit their levels typically decline over time. There is some proof that collagen dressings for venous leg ulcers are at the very least comparable to other modern wound dressings [**36**].

A glycoaminoglycan component of the ECM, hyaluronic acid has distinct biological and physical properties. Like collagen, hyaluronic acid is biocompatible, biodegradable, and naturally immune-suppressive. During the proliferative stage of wound healing, chitosan encourages the development of granulation tissue. Biological dressings are said to be more effective than other forms of dressings when compared to other dressings [**37**,**38**]. Alginates and chitosan have also been used successfully in a haemostatic dressing.

In a rat full-thickness wound model, it was demonstrated that sponges based on carboxymethyl chitosan, alginates, and a Chinese medication could quickly induce haemostasis and sustain wound closure. Lyophilisation and spray-drying procedures were used to create multi-resorbable haemostatic dressings made of chitosan, sodium/calcium alginate, and/or carboxymethyl cellulose. This kind of treatment was initially applied as a biological dressing to cover extensive burn wounds. Additionally, it has been used to heal chronic wounds, such as venous stasis ulcers [**39**]. Allografts from cadavers serve as a substrate for the formation of granulation tissue. The cadaveric skin is attached, an antibiotic/antimicrobial dressing is placed over the graft, and a compression dressing is used to lessen swelling once the wound bed has been prepped as previously mentioned. To enhance the physical and biological properties of tissue engineering products, such as wound dressings, chemical cross-linking is frequently utilised in the manufacturing process. Sodium trimetaphosphate, a secure and non-toxic cross-linking agent, can be used to improve the functional qualities of various polysaccharides, including starch, cellulose, and xanthan [**48**]. In patients with an ischaemic wound, biological wound dressing or topical agent therapy may hasten wound healing, increase limb salvage, be reasonably priced, and offer potential safety with nontoxic low-risk therapy. Therefore, patients with ischaemic wounds should also receive local wound care using biological dressings as an adjuvant therapy. To support the effectiveness and long-term results of these biological dressings in patients with ischaemic wounds, additional randomised studies are required [**49**].

### *4.9. Charcoal Dressings*

MDPI (/)

By absorbing gases produced by bacteria, activated charcoal dressings serve the primary purpose of reducing wound odour. They can absorb odour molecules due to their huge surface area and function as a deodorising agent. Wound odour is very subjective in nature since it is challenging to define and quantify. Leg ulcerations and diverse fungating lesions are the wounds most frequently linked to odour generation. Numerous aerobic bacteria as well as anaerobes including *Bacteroides* and *Clostridium* species are among the organisms usually linked to malodorous wounds [**51**,**52**,**53**]. Eliminating the problematic organism is the best strategy for treating wound smells. Antibiotics taken systemically may be successful, but it may be challenging to obtain an adequate concentration of the drug at the infection site. In numerous studies to date, topical treatments such as metronidazole, clindamycin, honey, and sugar have demonstrated promise in this area. Activated charcoal dressings are frequently used in malodorous wounds; however, odour control has not received as much attention in the literature as wound healing has. According to current clinical experiences, it is evident that these dressings can reduce wound odour, but there are not any hard facts on just charcoal ingredients [**56**,**57**,**58**].

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### *4.10. Three-Dimensional Skin Substitutes*

Recently, several tissue engineering technologies have become available; these technologies take a fundamentally unique and new approach. Among these, three-dimensional free-form fabrication—often referred to as three-dimensional bioprinting—offers several benefits over traditional skin tissue engineering. An innovative method for designing and engineering human organs and tissues is three-dimensional bioprinting, a flexible automated on-demand platform for the free-form production of complex living constructions. Here, we use human skin as a representative example to show the potential of three-dimensional bioprinting for tissue engineering. In order to simulate the epidermis, dermis, and dermal matrix of the skin, keratinocytes, fibroblasts, and collagen were employed as constituent cells [**154**]. This method has enormous potential for the creation of three-dimensional skin tissue since it can dispense living cells, soluble components, and phase-changing hydrogels in a desired pattern while preserving very high cell viability.

The biomimetic mechanical cues that support vascularisation, alignment of fibrous proteins in the ECM, integration of dermal and epidermal components, and adhesion between these layers are absent from the existing skin grafts and their production techniques. When the biomechanics of the repaired tissue at the wound site are compared to those of the healthy tissue nearby wounds, this problem may become more difficult. Therefore, to prevent the separation of the layers during application, a regenerative skin scaffold should take biomimetic mechanical cues into account. By adjusting the physicomechanical characteristics of each layer, the scaffold can offer tailored microenvironments for various cell types [**155**].

The use of autologous epidermal sheets as a kind of skin replacement has progressed into the use of more sophisticated bilayered cutaneous tissue-designed skin substitutes. However, their regular use for restoring normal skin anatomy is constrained by insufficient vascularisation, rigid drug/growth factor loading, and the inability to regenerate skin appendages such as hair follicles [**156**].

Recent developments in cutting-edge science from stem cell biology, nanotechnology, and other vascularisation techniques have given researchers a huge head start in creating and modifying tissue-engineered skin substitutes for better skin regeneration and wound healing. The creation of scaffolds for tissue engineering, films and membranes for wound healing, artificial tissues, and even artificial organs, all include the use of three-dimensional printing. Superior flexibility, regulated porosity, and reproducibility are the key benefits of the scaffolds made using this method. One of the current synthetic alternatives imitates the layer of skin made up of keratinocytes and fibroblasts on the collagen matrix. Only the dermal components with fibroblasts on the collagen matrix are present in the cellular matrix. Focused application, which stimulates wound healing and directs the healing of severe burns without scars, yielded encouraging results.

Bioengineered organisms can adjust to their surroundings and release the growth factors and cytokines used in dressings. Both venous leg ulcers and diabetic foot ulcers can be treated using bioengineered dressings. The additive manufacturing method of three-dimensional bioprinting offers a viable method for creating biocompatible artificial skins by carefully layering growth factors, biomaterials, and living cells on top of one another. This automated technology is a versatile tool that, in terms of accuracy and usefulness, is ideal for therapeutic usage. Through the exact deposition of many cells and biomaterials, the bioprinted skin analogues closely replicate the native skin's architecture and heterogenicity [**157**]. The bioprinted skin constructions need to meet several requirements in terms of their compositional and functional qualities. The ability to transmit nutrients and wound exudates should be the first feature of bioprinted skin substitutes. The ability to precisely deposit various skin cells, such as keratinocytes, fibroblasts, adipocytes, melanocytes, Langerhans cells, etc., at certain layers and places is another requirement for bioprinted analogues. Finally, the bioprinted structure needs to be strong, biocompatible, biodegradable, and able to withstand the external forces and pressures that are present under in vivo circumstances. Despite revolutionising wound treatment, skin replacements have several drawbacks. They necessitate lengthy cell culture processes that extend production times. Most of the vascularisation is inadequate. Scarring occurs at the graft margins, which exacerbates existing functional and aesthetic issues. Infection is always a possibility. Since they only have fibroblasts and keratinocytes, they are unable to develop differentiated structures including sweat and sebum glands, hair follicles that cycle, pigmentation, sensory innervation, and motor innervation, as well as the epidermal barrier and dermal–epidermal junction

[39,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100,101,102,103,104,105,106,107,108,109,110,111,112,113,114,115,116,117,118,119,120,121,122,123,124,125,126,127,128,129,130,131,132,133,134,135,136,137,138,139,140,141,142,143,144,145,146,147,148,149,150,151,152,153,154,155].

Porosity, degradation, and mechanical properties should closely resemble the native skin structure. Onto a scaffold made of hyaluronic acid in three dimensions, autologous cultured fibroblasts are sown. Apligraf, a skin substitute for venous ulcers made from keratinocytes and fibroblast-seeded collagen, has received FDA approval [156,157]. Commercially available skin substitutes include IntegraTM artificial skin, which is made of a collagen/chondroitin-6-sulphate matrix coated with a thin silicone sheet, and AllodermTM, which is made of normal human fibroblasts with all cellular components removed. LaserskinTM, BiobraneTM, BioseedTM, and Hyalograft3-DTM are a few further alternatives.

*4.11. Dendrimers*

Dendrimers are a class of nanoscale (1–100 nm) three-dimensional globular macromolecules with numerous arms branching out from a central core. They have unique structural characteristics, including high levels of branching, multivalency, globular architecture, and well-defined molecular weight, making them promising drug delivery scaffolds. The distinctive structure of dendrimers makes them an ideal nanomaterial for the administration of medications to target certain tissues or molecules with solubility challenges. This is performed by trapping the drugs inside of their void spaces, branches, or outside functional groups. An expanding field of research involves cross-linking collagen with functionalised nanoparticles to produce scaffolds for use in wound healing. Due to their spherical structure, dendrimers can engage via hydrogen bonding, lipophilicity, and charge interactions with tiny medicines, metals, or imaging moieties that can fit within their branches. In addition to their structure, dendrimers may be the best drug delivery vehicles for many therapeutic treatments because of their size and lipophilicity, which allow them to easily permeate cell membranes. These distinguishing qualities have increased interest in using dendrimers nanoparticles for wound healing in research [158].

In order to build an efficient nanoparticle-mediated scaffold for tissue engineering and wound healing applications, Vedhanayagam et al. showed that nanoparticle form is a critical component that needs to be investigated. The re-epithelialisation and collagen deposition in damaged tissue are accelerated more quickly by the spherical shape of zinc oxide triethoxysilane poly(amidoamine) dendrimer generation 1 nanoparticles than by other shapes. The highly branched 3D structures known as antimicrobial peptide dendrimers (AMPDs) have a central core and a high density of flexible surface

groups for possible molecule attachment. Their capacity to penetrate the cell membrane and the presence of functional groups of amino acid residues are what cause them to have bactericidal effects [**159**].

Mannose-decorated globular lysine dendrimers have the ability to reduce inflammation by targeting and reprogramming macrophages to the M2 phenotype, which is characterised by significant mannose receptor clustering on the cell surface and the elongated shape; increased production of TGF-1, IL-4, and IL-10; decreased secretion of IL-1, IL-6, and tumour necrosis factor (TNF); and increased ability to induce fibroblast proliferation. These results show that M2 macrophage polarisation can be directed by mannose-decorated globular lysine dendrimers, which may be helpful in the treatment of injuries and inflammation [**160**].

The development of an antisense delivery method based on dendrimers has assisted in the development of an antisense therapy strategy to treat bacterial infections. Dendrimers themselves might function as powerful antibacterial substances. In contrast, those with metal cores can produce active antimicrobial agents such as metal ions and ROS, which can kill bacteria. For example, those with positively charged surfaces typically have significant interactions with negatively charged bacterial cell membranes. AgNPs may benefit from the alternate template that dendrimers can offer. Dendrimers have a stronger antibacterial action when combined with silver than silver has by itself. In computerised tomography or immune-sensor coatings, poly-(amido-amine) dendrimers have been utilised as contrast agents. These highly branched dendritic molecules have a restricted size range, a well-defined globular structure, and a relatively large molecular mass [**161**].

Among the family of monodisperse, highly branched units with a clearly defined structure are dendrimers such as poly(amidoamine). Their surface contains a cationic primary amine group, which enables them to participate in chemical bonding. For the treatment of wounds, poly-(amido-amine) dendrimers are primarily used as a vector for the transport of various hydrophilic or hydrophobic medicines and genes. The hesperidin-loaded dendrimer was found to be biocompatible and suitable for use in wound healing after a haemolysis investigation [**162**]. Tumour suppression applications have demonstrated the anti-angiogenic properties of polycationic dendrimers. Angiogenesis and neovascularisation, however, are important components for skin regeneration following serious burn wounds because newly created blood vessels aid in the healing process by improving nutrition and oxygen supply to regenerating tissues. Therefore, using polycationic antimicrobial peptide dendrimers could prevent angiogenesis and endanger the process of skin regeneration [**163**].

Dendrimers are incorporated into gelatin nanofibres through covalent conjugation, which not only increases the capacity of nanofibre construction for drug loading but also offers a great deal of versatility for creating multipurpose electrospun dressing materials. Since dendrimer–gelatin nanofibre constructs are designed to treat a variety of wounds, including chronic wounds,

burns, and skin malignancies, they can be customised to offer cutting-edge therapies [**164**,**165**]. Dendrimers have a variety of uses in biomedicine, but their toxicity has also been described in order to analyse the restrictions on their use. The structure of a chemical determines its toxicity as well as all of its other characteristics. A dendrimer's toxicity can either be increased or decreased depending on specific components (core, branch, and surface groups) [**158**,**161**].

*4.12. Carbon Nanotubes*

The carbon nanotubes are a class of stiff, stable, hollow nanomaterials with a variety of special physical, chemical, and mechanical properties that have been widely used as catalyst supports, nanowires, electronic components, and more recently in the fields of biomedical engineering and medical chemistry [**166**]. A needle-like structure with a significant surface area, carbon nanotubes are an allotropic form of carbon with nanoscale dimensions and μm lengths. The carbon atoms join to form sheets of graphite, which is made up of six-membered carbon atom rings. Graphite then spirals into tubes. Carbon nanotubes can be divided into single-wall and multiwall varieties based on the number of graphite layers present. CNTs have tensile strengths up to 63 gigapascals, which is around 50 times stronger than steel, and elastic moduli between 1.0 and 1.8 terapascals. With the goal of boosting drug delivery, regulating drug release, and improving therapeutic activity, carbon nanotubes are now being functionalised by various pharmacologically active compounds, with some degree of success [**167**]. The degradation products of carbon nanotubes can be eliminated by the functional tissues of the human body, making them non-toxic and safe for consumption [**168**]. The fibroblasts, which are crucial to the cell renewal system and the healing process of open wounds, may come into contact with the carbon nanotubes employed in the biomedical field and found in the environment as they pass through the skin or open wounds [**166**]. Proteins and receptors found in cell membranes can cling tightly to carbon nanotubes. Carbon nanotubes and cells must adhere to one another [**166**].

The ability of organic compounds with a carbon component to improve the antibacterial activity of polymers is well known. Because they can function as a conductive bridge over the insulating bilayer, carbon nanotubes' antimicrobial activity can be increased following functionalisation with -OH and -COOH functional groups or hybridisation with metallic compounds. After being incorporated into chitosan biopolymers, multiple-walled carbon nanotubes boost cell survival and proliferation with few negative side effects. Using the solution casting technique, Liu et al. created a bio-nanocomposite film-based wound healing dressing. The film's ability to absorb water is crucial to preventing tissue dehydration, limiting the growth of microorganisms, and safeguarding wound maceration. It is anticipated that the multiple-walled carbon nanotubes' hydrophilic nature and water-holding capacity will increase the bio-nanocomposite film's ability to absorb water. Through chemical interactions, the presence

of multiple-walled carbon nanotubes increases ROS formation [**169**]. The physical properties of fibrous proteins found in the ECM, such as collagen and elastin, are approximated by the greater diameter of multiple-walled carbon nanotubes compared to single-walled carbon nanotubes.

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According to molecular research conducted by Khalid et al., bacterial cellulose functionalised with multiwalled carbon nanotubes displayed a lower than control level of pro-inflammatory cytokines IL-1 and TNF- and a higher level of VEGF expression, which may have favoured a quicker healing process [**170**]. Carbon nanotubes may pass through a variety of physiological barriers and have substantial tissue penetration. Isoniazid/chitosan/carbon nanotube nanoparticles were created by Chen et al. and have been shown to dramatically speed up the healing of tuberculosis ulcers [**171**]. Experimental tests demonstrated by Zhao et al. revealed that the antibacterial gel made of nano-silver and multiple empty carbon nanotubes has a superior anti-infective impact on burn wounds and can significantly lessen the frequency of dressing changes [**172**]. By affecting cell spreading, adhesion, migration, and survival, exposure to carbon nanotubes causes inflammation, genotoxicity, and inhibits dermal fibroblasts' capacity to heal wounds. While concurrently harming the cytoskeleton and upsetting actin stress fibres in NIH 3T3 murine fibroblasts and human dermal fibroblasts, multiwalled carbon nanotubes reduced DNA synthesis and the levels of adhesion-related genes. Skin allergies are made worse, and keratinocyte cytotoxicity is also produced, by low doses of topical multiwalled carbon nanotubes [**166**,**167**,**168**,**169**].

### *4.13. Microneedle Drug Delivery Systems*

The efficacy of traditional single-drug therapies is subpar, and penetration depth limits the effectiveness of drug delivery [**173**]. In the realm of wound healing, microneedle dressings with transdermal drug delivery capabilities have been crucial [**174**]. Additionally, the microstructure of microneedles allows for efficient medication administration to the target location while preventing overly strong skin and patch adherence. Additionally, temperature-sensitive hydrogel has been used to encapsulate vascular endothelial growth factor (VEGF) in the chitosan microneedle array micropores. As a result, the temperature increase brought on by the inflammatory response at the site of wounds can be used to controllably achieve the smart release of the medications [**175**]. The adaptable approach of the microneedle patch has been presented and has achieved several outstanding successes in the fields of disease therapy, biosensing, skin vaccination, and wound healing. Microneedles can efficiently deliver the desired active pharmaceuticals due to their better loading capacity and well-designed microstructures when compared to those used in conventional drug delivery systems. However, the microneedle that is so frequently used today is typically made from synthetic polymer materials that were created by difficult chemical synthesis using harsh

experimental processes and environmentally hazardous organic reagents. This raises the danger of side effects. Additionally, the development of microneedle-based iatrotechnics is constrained by the acquisition of loaded active pharmaceuticals typically through a period of brutal elimination and extremely stringent clinical studies [**176**]. Wang et al. created a three-dimensional origami microneedle patch with extremely tiny needle structures, microfluidic channels, and numerous functionalities that was said to be able to detect biomarkers, distribute medications in a controlled manner, and monitor motions to speed up wound healing [**177**]. Exosomes can only partially reach the injury site through passive diffusion, according to Liu et al.'s explanation of the potential of microneedle delivery of exosomes for transdermal application [**178**]. As a result, the therapeutic effects and clinical applications are significantly diminished. An antibacterial and angiogenesis-promoting double-layer microneedle patch was reported by Gao et al. for the treatment of diabetic wounds. Tetracycline hydrochloride, an antibacterial medication filled with hyaluronic acid, serves as the tip of the double-layer microneedle, while deferoxamine, an angiogenic medication, serves as the substrate [**179**]. The transdermal route has been used to administer bioactives using microneedles. The bioactives can pass through the epidermis with the assistance of these microneedle devices. Microneedles are created via in situ polymerisation utilizing a mould-based approach using biomaterials such as chitosan, hyaluronic acid, and maltose [**180**]. In the realm of wound management, new individualised and programmable microneedle wound dressings are extremely valuable. With its straightforward, efficient, and safe qualities, the microneedle-mediated drug delivery system can also offer a novel method for the treatment of diabetic wounds. It has a wide range of applications in relevant biomedical sectors. The low stiffness of the microneedles for insertion into human skin poses a challenge for the translation of this method. The constraints and high cost of microfabrication technology have restricted the development of microneedle-based systems utilising standard subtractive techniques [**181**,**182**].

## 5. Future Prospects

The alignment of fibrous proteins, cell type, ECM composition, water content, and mechanical qualities vary between skin layers. However, the skin's natural ability to regenerate is constrained to treating relatively small wounds, necessitating the use of topical medications in some or most cases. Therefore, because the healing process entails complicated events to re-establish functional tissues following injury, big skin wounds present a problem. Due to the existence of several cells and chemicals orchestrating a process, wound healing has always been the most difficult problem. Any problem may hinder the healing process and cause an acute wound to become chronic. The difficulty in keeping immune cells in their naive immune

state is currently a major barrier to their incorporation in the skin, and it is probably due to their ineffective incorporation within the skin strata as well as the absence of other functionally significant cells. Adult stem cells have emerged as a promising therapy for promoting scarless wound healing among the numerous techniques that have so far been used in the treatment of skin ulcers. Mesenchymal stem cells have drawn more attention than other adult stem cells due to their capacity for immunomodulation and tissue regeneration. Intense research is still being conducted on the creation of novel and efficient therapies for wound care. Future topical therapy for wound care can be evaluated using comparative effectiveness research as a technique. Over the past ten years, a number of novel techniques and items have been developed, helping to meet the ongoing demand for advancements in wound care. Numerous other techniques, including hyperbaric oxygen, growth hormones, biologic dressings, skin substitutes, and regenerative materials, have also demonstrated effectiveness in speeding up the healing of wounds.

## Author Contributions

Conceptualization, R.T. and K.P.; validation, R.T.; resources, R.T. and K.P.; writing—original draft preparation, R.T.; writing—review and editing, K.P.; supervision, K.P. All authors have read and agreed to the published version of the manuscript.

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## Conflicts of Interest

The authors declare no conflict of interest.

## Abbreviations

AgNPs: Silver nanoparticles; AMPDs: Antimicrobial peptide dendrimers; AuNPs: Gold nanoparticles; CAT: Catalase; CNTs: Carbon nanotubes; CTGF: Connective tissue growth factor; ECM: Extracellular matrix; EGCG: Epigallocatechin-3-gallate; EGF: Epidermal growth factor; EGR1: Early-growth response 1; ELAM-1:Endothelial leukocyte adhesion molecule 1; FGF-2: Fibroblast growth factor -2; GPX: Glutathione peroxidase; HIF-1: Hypoxia-Inducible Factor; ICAM-1: Intercellular adhesion molecule 1; IGF-1: Insulin-like Growth Factor-1; IL-1: Interleukin-1; IRF5: Interferon regulatory factor 5; LOX-1: Lectin-like oxLDL (oxidised low-density lipoprotein); MAPK: Mitogen-activated protein kinase; MCP-1: Monocyte Chemoattractant Protein-1; MMP-1: Matrix metalloproteinase-1; MRSA: Methicillin-resistant *Staphylococcus aureus*; mTOR: mammalian target of rapamycin; ORC: Oxidised regenerated cellulose; PDGF: Platelet-derived growth factor; pNFκB: Phospho-Nuclear Factor Kappa B; PPAP: Polyprenylated acylphloroglucinol; pSTAT1:Phosphosignal transducer and activator of transcription 1; ROS: Reactive oxygen species; SMAD: Suppressor of Mothers against Decapentaplegic; SOD: Superoxide dismutase; TGF- β: Transforming Growth Factor-beta; TLR: Toll-like receptors; TNF-α: Tumour Necrosis Factor Alpha; VCAM-1:Vascular cell adhesion molecule 1; VEGF: Vascular endothelial growth factor; VPF: Vascular Permeability Factor.

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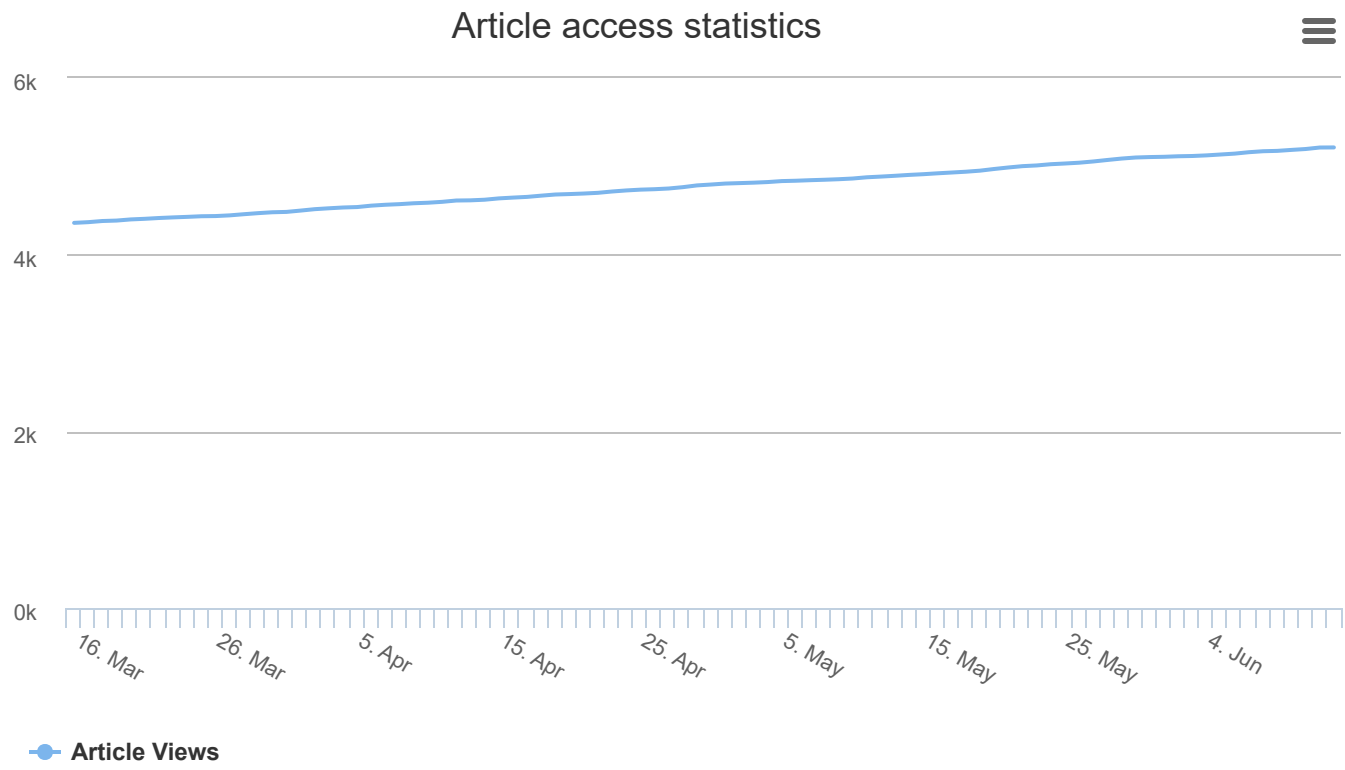
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# Lipid–Polymer Hybrid Nanosystems: A Rational Fusion for Advanced Therapeutic Delivery

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## Abstract

Lipid nanoparticles (LNPs) are spherical vesicles composed of ionizable lipids that are neutral at physiological pH. Despite their benefits, unmodified LNP drug delivery systems have substantial drawbacks, including a lack of targeted selectivity, a short blood circulation period, and in vivo instability. lipid–polymer hybrid nanoparticles (LPHNPs) are the next generation of nanoparticles, having the combined benefits of polymeric nanoparticles and liposomes. LPHNPs are being prepared from both natural and synthetic polymers with various techniques, including one- or two-step methods, emulsification solvent evaporation (ESE) method, and the nanoprecipitation method. Varieties of LPHNPs, including monolithic hybrid nanoparticles, core–shell nanoparticles, hollow core–shell nanoparticles, biomimetic lipid–polymer hybrid nanoparticles, and polymer-caged liposomes, have been investigated for various drug delivery applications. However, core–shell nanoparticles having a polymeric core surrounded by a highly biocompatible lipid shell are the most commonly explored LPHNPs for the treatment of various diseases. In this review, we will shed light on the composition, methods of preparation, classification, surface functionalization, release mechanism, advantages and disadvantages, patents, and clinical trials of LPHNPs, with an emphasis on core–shell-structured LPHNPs.

**Keywords: lipid–polymer hybrid nanoparticles (/search?q=lipid%E2%80%93polymer+hybrid+nanoparticles)**; **cancer (/search?q=cancer)**; **drug delivery (/search?q=drug+delivery)**; **synthesis (/search?q=synthesis)**; **release mechanism (/search?q=release+mechanism)**

## 1. Introduction

Nanoparticles (NPs) made of either polymers or lipids are widely used for the delivery of therapeutic agents. Polymeric nanocarriers are chiefly categorized as polymeric micelles, polymer–drug conjugates, and polymeric NPs, while lipid-based nanocarriers are distinguished as liposomes, solid lipid nanoparticles (SLNs), and nanostructured lipid vectors [**1**,**2**]. Polymeric nanoparticles (PNPs) are currently gaining popularity in biomedical research, possibly due to their numerous attractive properties, including biocompatibility, biodegradability, the ease of processing, and sustained release patterns of incorporated drugs [**3**]. PNPs are easy to prepare with simple and reproducible synthesis processes, with ample flexibility for chemical modifications [**4**]. Polymeric NPs usually have low polydispersity and high stability. However, there are certain limitations associated with using polymers as nanocarriers for drug delivery, for instance, the use of harmful organic solvents in the preparation, the expensive synthesis, the scale-up process, the toxicity of degradation products, and the usually low drug loading capacity [**5**,**6**]. Moreover, the hydrophobic surface of PNPs is recognized as a foreign material that provokes an immune response and prompts rapid elimination from the body, which limits their use. Furthermore, the limited cellular membrane permeability of PNPs leads to poor transfection efficiency [**7**,**8**].

Lipid nanoparticles, similar to PNPs, have piqued the interest of researchers in recent decades and have had remarkable clinical success in delivering drugs, nucleic acids, and vaccines. Lipid nanoparticles offer numerous attractive benefits, including low production costs with an ease of preparation, an improved drug-entrapping efficiency, great biocompatibility, feasibility of scale-up, and targeted delivery. However, they have abridged stability, fast drug release, and excessive polydispersity, which are the major limitations for their widespread use [**9**,**10**,**11**].

To overcome these limitations of PNPs and lipid nanoparticles, a new system called lipid–polymer hybrid nanoparticles (LPHNPs) has been developed owing to the biomimetic and biocompatible advantages of this strategy. LPHNPs take advantage of the benefits of both polymeric and lipid-based systems [**12**]. LPHNPs are next-generation core–shell nanosystems conceptually formed from a polymer core wrapped by a lipid layer. Despite their widespread attention, they are not yet widely used or pervasive [**13**]. LPHNPs have three structural features, including (**Figure 1**):

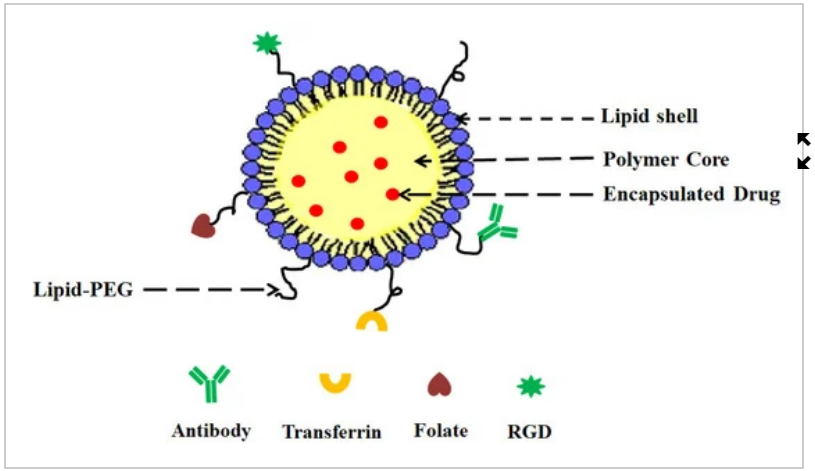



**Figure 1.** General structure of LPHNP composed of a drug-encapsulating polymer core with an outer lipid shell and an outer lipid–PEG layer.

(i) A drug encapsulating polymer core;
(ii) A lipid layer surrounding the polymer core;
(iii) An outer lipid–PEG layer.

The lipid layer acts as a molecular barrier, reducing drug loss during LPHNP formulation and further protecting the core from degradation by blocking water diffusion into the inner core. The outer lipid–PEG layer prolongs the blood circulation of LPHNPs by suppressing the immune response [**14**].

## 2. Advantages and Limitations of LPHNPs

LPHNPs combine the benefits of polymeric nanocarriers, such as favorable drug release profiles and surface chemical functionalization or modification; with the benefits of lipid-based nanocarriers, such as improved drug loading capacity and biocompatibility [**15**,**16**,**17**]. Recent research trends indicate that LPHNPs will, for instance, be extremely helpful or productive in the treatment of diseases such as glioblastoma [**18**]. LPHNPs offer the advantage of being able to select the polymer for a controlled drug release using stimuli-responsive polymers. The outer lipid layer prevents the inner polymeric materials from leaking and seizes the water penetration from the outside to the inside. Such a framework ensures that the formulation is

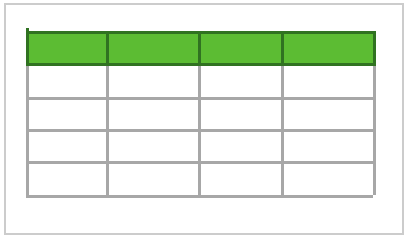
continuously resilient for maximal structural integrity. The lipid-layer coating improves the biocompatibility and stability of NPS upon systemic administration. In comparison to the individual polymer and lipid particles, the LPHNPs have been reported to have a better and longer in vivo efficacy [**19**]. Although LPHNPs have advantages over PNPs and liposomes, significant drawbacks reduce their translational rate from bench to bedside. It is challenging to optimize the lipid/polymer ratio within NPs [**20**]. The change in lipid/polymer (L/P) composition during prolonged storage leads to drug leakage. Since phospholipids form the micellar phase while polymers form the nanoparticle phase, this may lead to an increase in the polydispersity, which may result in destabilization, agglomeration, and phase separation. Hydrophilic drug loading into the LPHNP matrix is often limited, which can be overlooked by using the double emulsification method to improve the drug loading characteristics, but it is a time- and energy-consuming method [**21**,**22**]. To avoid phase separation, the affinity of the phospholipid to create a monolayer over the polymeric nanoparticle surface must be considered during the phospholipid and polymer selection process. The bulk synthesis of LPHNPs is currently difficult to scale up; nevertheless, a few attempts have been reported, employing microfluidics or multi-inlet vortex reactors [**23**]. The higher cost of LPHNPs might be due to additional fabrication steps, and the use of both lipids and polymers could incur patient unacceptance [**24**]. Because of the use of solvents and excipients during fabrication, the environmental impact of LPHNPs synthesis must be carefully considered. The interaction of LPHNPs with plasma proteins must be assayed to examine the modifications required for the pharmacokinetic and pharmacodynamic profiles. The major barrier to gain approval for LPHNPs for human use is the lack of regulatory guidelines [**25**].

## 3. LPHNPs Composition and Its Influence

LPHNPs composed of natural, semi-synthetic, and synthetic polymers (i.e., chitosan, PCL, polycaprolactone; PEG, polyethylene glycol; PLA, polylactic acid; PLGA, polylactic-co-glycolic acid; PbAE, poly(β-amino ester); etc.) serve as solid core NPs coated with lipids (i.e., palmitic, myristic, and stearic acids, etc.). The simplest design of LPHNPs has a drug-entrapped hydrophilic or hydrophobic polymer core surrounded by a lipid layer. Lipid shells can be easily modified to obtain the desired surface properties which promotes, for instance, efficient uptake, controlled drug release, and favorable biodistribution. The lipid composition can be easily modified and exploited to expedite the covalent or noncovalent attachment of drugs, ligands, transferrin, antibodies, folic acid, aptamers, and bioactive molecules, including nucleic acids or proteins. Lipid shells have the additional advantage of charged or zwitterionic lipids, which may promote self-assembly of the lipid layers with opposite charges on the polymeric core through electrostatic interactions. Likewise, the uses of the lipophilic core endorse its interaction

with the hydrophobic tail domain of the lipids constituting the lipid layer [**26**]. **Table 1** presents the polymers and lipids used in the preparation of LPHNPs.

**Table 1.** Commonly used polymers and lipids for the preparation of LPHNPs with their structures.



Polymer aggregation and intrinsic viscosity have a direct influence on the particle size. Higher polymer concentrations yield larger particles, while polymers with a higher intrinsic viscosity produce smaller particles [**38**]. The surface zeta potential of LPHNPs can be altered by changing the end functional groups on shells (usually PEG). Because surface charges prevent particles from colliding, higher absolute zeta potential values result in more stable NPs in vitro. Dave et al. [**39**] reported that on increasing the concentration of soy lecithin from 20 mg to 30 mg, the zeta potential of the prepared LPHNPs also increased from 23.4 ± 1.5 mV to 41.5 ± 3.4 mV. Furthermore, the interaction of charge inducer (i.e., stearyl amine, SA) with the lipid surface also alters the zeta potential of formulations. According to immunocompatibility tests, the complement activation is the lowest in hybrid NPs with methoxyl surface groups and the highest in NPs with amine surface groups [**40**]. An adequate surface charge must be chosen to match the hybrid NPs in vitro stability and in vivo immunocompatibility. The lipid-to-polymer ratio (L/P) had a significant impact on the colloidal stability of hybrid particles. The lipid layer may operate as an electrostatic stabilizer when the lipid-to-polymer L/P ratio is high and the cationic lipid concentration is high. At low L/P and cationic lipid fractions, the partial lipid coating of the polymer core was inadequate to colloidally stabilize the LPHNPs. For example, when the anionic surface of one hybrid molecule core was exposed to the cationic 1,2-dipalmitoyl-3-trimethylammonium-propane, LPHNPs aggregation occurred. Surprisingly, when 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC) was employed alone, the hybrid NPs were less prone to agglomeration. This is because the DPPC's zwitterionic structure lowers the possibility of electrostatic interactions [**41**].

Poly(lactic acid) (PLA) is a biopolymer that has gained more attention because of its both biodegradable and biocompatible nature. Because of its high safety profile, the US Food and Drug Administration (US FDA) has approved it for a

variety of purposes. For almost two decades, LP-anchored PLA NPs have been employed to deliver medicines, peptides, and vaccinations [**42**]. The greater mechanical stability of LPHNPs during storage and in serum is attributed to the polymeric core, which behaves as cytoskeleton and to a PEG-coated lipid layer, which improves blood circulation time in vivo by suppressing the immune system [**43**]. However, the low cell interaction leads to a poor drug delivery efficiency, which is the major limitation. The problem can be resolved by coating or attaching a site-specific target ligand with an outer lipid layer of NPs to mimic the binding with cell surfaces and deliver the payload. The biomimetic LPHNPs retain both the physicochemical features of the synthetic vehicles and inherit the intrinsic functionalities of the cell membranes [**44**].

Lipids are amphiphilic or hydrophobic molecules and are present in numerous compounds, including fatty acids, oils, steroids, and waxes. Glycerophospholipids are the most common type of biological membrane component, consisting of a glycerol molecule, a phosphate group ($PO_4^{2-}$), and two fatty acids. These phospholipids are broadly used for the surface engineering of PNPs. Phospholipids, including phosphatidylcholine, phosphatidylglycerol, phosphatidylinositol, phosphatidylserine, phosphatidylethanolamine, and phosphatidic acid are less stable in nature. Thus, synthetic lipids have been reported through the modification of the polar and nonpolar regions of the phospholipid molecules. Synthetic phospholipids, including PEGylated phospholipids, 1,2-diacyl-P-O-ethylphosphatidylcholine, etc., are cationic, anionic, neutral, and zwitterionic phospholipids and are often used in biomedical engineering [**45**]. Both natural and synthetic lipids have been used for the surface anchoring of PNPs. Natural or cell-membrane-derived lipids have the advantages of natural cell surface, natural targeting ability, natural immune-evading property, long circulating half-life, and well-controlled tissue distribution. Synthetic lipids have the advantages of biomimetic surface, controlled drug release, stealth properties, extended circulation, and surface flexibility for targeting functionalization [**41**].

The lipid-based surface functionalization of PLGA NPs is showing encouraging outcomes in the fabrication of PLGA-based nanomedicines due to their fascinating properties of biocompatibility, biodegradability, ease of treatment, and sustained release. The targeting specificity of PLGA-based nanocarriers can be enhanced by surface engineering with various lipids. This may further improve the physicochemical properties of nanocarriers as well as their NP–cell associations, including cellular membrane permeability, immune responses, and prolonged blood circulation. PLGA-based LPHNPs have been reported to be utilized for drug and gene delivery [**46**].

## 4. LPHNP Fabrication Methods

LPHNPs have been prepared traditionally by a simple two-step method, but nowadays, a transformation strategy has been introduced that transitions a two-step LPHNPs preparation to a one-step strategy. The latter technique synchronously uses the self-assembly of polymers and lipids. Owing to their two-in-one structure, these LPHNPs are used for combinatorial drug delivery, especially in oncology. The outer lipid–PEG layer can be tailored in such a fashion to achieve the targeting of anticancer therapy, delivery of nucleic acids, and to be used in diagnostic imaging. Although the fusion mechanism of lipid and polymer is still unclear, methods of LPHNP preparation that utilize different mechanisms of formation are presented in **Figure 2** [47].

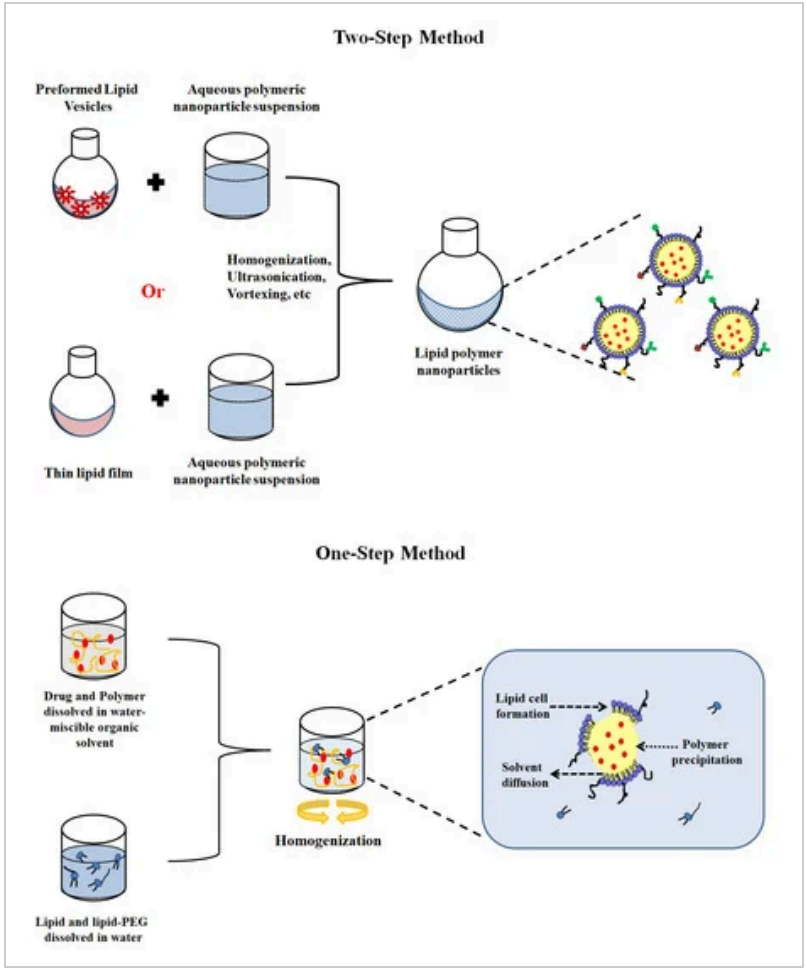


**Figure 2.** Single- and two-step methods for the preparation of LPHNPs.

In the two-step method, the LPHNPs are produced by either directly adding the aqueous polymeric nanoparticle suspension to the dried lipid film or first hydrating the thin lipid film with an aqueous solvent to produce lipid vesicles, and then these lipid vesicles are added to an aqueous preformed nanoparticle suspension [**48**]. In both methods, the hybrids are assembled by the input of external energy provided via vortexing or through the ultrasonication of the suspension and heating at a temperature beyond the phase transition temperature of the lipid constituent. The prepared hybrid structure is thermodynamically stable via electrostatic, hydrophobic, and van der Waals interactions [**49**].

In the single-step method, the drug and polymer solution in a water-miscible organic solvent is added to an aqueous medium encompassing lipids or lipid–PEG, with spontaneous homogenization, resulting in self-assembly into a monolayer of lipids surrounding the core. During this stage, PEGylated lipids are also self-assembled, with a lipid moiety clinging to the surface of the polymer core and the PEG chain extending externally toward the aqueous environment [**50**].

The two-step method has the limitation of formulating PNPs and lipid vesicles separately, which requires more energy and is a more time consuming process. The single-step or one-step method is more prevalent and efficient as lipid vesicles and PNPs are not prerequisites in this method. In this method, the spontaneous self-assembled monolayer formation occurs, surrounding the core to form LPHNPs; therefore, it is a rapid and energy-efficient technique [**51**].

The emulsification solvent evaporation (ESE) method is another technique for the preparation of LPHNPs. This method is further classified into single and double emulsification methods. In the single ESE method, hydrophobic drugs and polymers dissolved in the oil phase are mixed with an aqueous phase containing lipids under constant agitation to form an oil-in-water (o/w) emulsion. The evaporation of the organic medium simultaneously forms a polymer core surrounded by a lipid layer. As an apparent substitute, the lipid can be dissolved in the oil phase alongside the polymer [**52**]. For water-soluble formulations, the double ESE method is employed to prepare w/o/w emulsion. In this method, the aqueous drug solution is emulsified in an organic solvent that contains polymers and lipids to form a w/o mixture. The prepared w/o mixture was further emulsified in a lipid–PEG-containing aqueous phase to form a w/o/w emulsion, followed by subsequent oil phase evaporation to produce LPHNPs (**Figure 3**) [**53**]. The LPHNPs produced by the double ESE method have certain structural anomalies, including: (1) aqueous core surrounded by a lipid layer; (2) a polymer layer in between; and (3) an outer lipid–PEG shell.

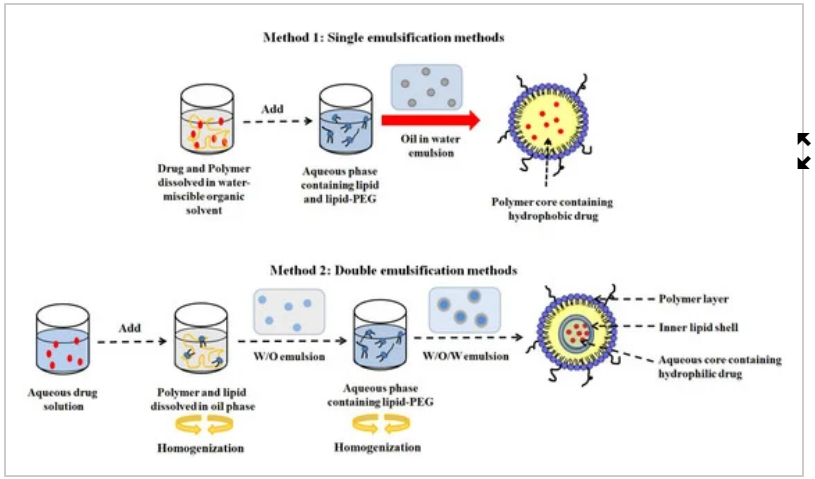



**Figure 3.** LPHNPs produced by single and double emulsion-solvent evaporation (ESE) methods.

On the basis of the desired biomedical applications of LPHNPs, a lipid-based surface engineering method is to be chosen, which further depends on the nature of lipid–polymer surface chemistry. For example, the single-step ESE method is used for gene delivery applications, while the conventional two-step top-down approach is required for nanoghost-based surface engineering [**54**].

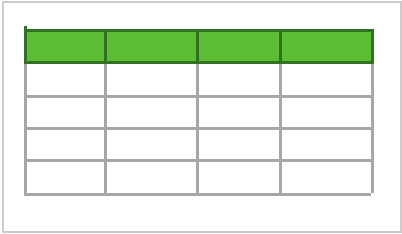
Nanoprecipitation technique is another method for the preparation of LPHNPs. This technique utilizes the dispersion of lipids in the aqueous phase followed by the addition of a drug–polymer solution in a water-miscible organic solvent with sonication, stirring, or homogenization. This causes the polymer to precipitate via solvent diffusion, as well as the lipid to self-assemble onto the polymeric nanoparticle interface [**55**]. The nanoprecipitation approach was used to prepared triptolide (TL)- and paclitaxel (PTX)-loaded LPHNPs for lung cancer treatment [**56**]. Prepared LPHNPs were approximately 160 nm in size with a 0.2 polydispersity index. Both drugs showed a greater encapsulating efficiency of about 85%, and the in vivo results revealed around a four-fold reduction in tumor volume as compared with the control group (i.e., PTX and TL). The findings indicate synergy as well as a greater efficiency in treating lung cancer. To achieve a homogenous liquid crystalline phase, the temperature must be kept above the gel-to-sol temperature of lipids during the synthesis. The lipid–aqueous phase acts as an anti-solvent (above their transition temperature) toward a dropwise injection of polymer in organic solvent, resulting in the polymer to aggregate and coil, followed by a self-assembly of lipids surrounding the polymeric core.

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Lipid/polymer ratio plays an imperative role in the synthesis of LPHNPs. As the phospholipid concentration rises over the critical micelle concentration, liposomes form, while decreasing the L/P ratio causes agglomeration due to the anti-solvent impact of the aqueous phase, which reduces lipid content for interfacial stabilization. Furthermore, the use of PEGylated lipids increases the colloidal stability of hybrid NPs. Because of the steric stabilization provided by PEG chains, the PEGylated lipid increases stability without interfering with drug loading and release.

Numerous LPHNP studies are listed in **Table 2**, describing the preparation methods of LPHNPs, encapsulating materials, targeting ligands, physicochemical properties, and their applications.

**Table 2.** Summary of recent published studies on LPHNPs.



On the basis of structure differences, LPHNPs can be classified as: (i) monolithic hybrid nanosystems, having a polymeric matrix in which lipid molecules are dispersed randomly [**44**]; (ii) core–shell nanosystems, having a polymeric core surrounded by a highly biocompatible lipid shell [**109**]; (iii) hollow core–shell NPs, having a hollow inner aqueous core surrounded by an inner polymer layer and cationic and neutral lipid layers [**110**]; (iv) biomimetic lipid–polymer hybrid nanosystems, having a polymer layer anchored on the surface of liposomes [**111**]; and (v) polymer-caged liposomes, having a polymer layer surrounded by a biomimetic (**Figure 4**).

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**Figure 4.** A graphical representation of different types of LPHNPs.

## 5. Surface Functionalization of LPHNPs

Surface anchoring is an important and crucial aspect for ameliorating the pharmacokinetics (PKs) and pharmacodynamics (PDs) of LPHNPs. PEGylation of lipids (PEG-lipids) on the outer shell improves blood circulation time but diminishes cell internalization [**112**,**113**]. Changing the surface charge, zeta potential, and lipophilicity alters the cell uptake of LPHNPs as well as alters the PK-PD profile of numerous drugs. Surface functionalization imparts target-specific intracellular localization and reduces toxicity. Surface functionalization can be achieved by tethering small molecules, antibodies, cell-penetrating peptides, and aptamers (**Figure 5**).

**Figure 5.** The representation of different surface-anchoring possibilities with LPHNPs.

Clawson et al. [**114**] prepared pH-triggered PEG-shedding LPHNPs. To make the LPHNPs pH sensitive, a lipid-(succinate)-methoxy-PEG (mPEG) conjugate was prepared that was highly sensitive to acidic hydrolysis and provided a hydrolyzable PEG stealth layer. The lipid-(succinate)-mPEG conjugate hydrolyzes via diester succinate. The pH sensitivity of the NPs can be adjusted by changing the molar concentration of lipid-(succinate)-mPEG in the lipid shell. The more lipid-(succinate)-mPEG integrated into the particle lipid shell, the more stable the particles are at low pH. Thus, by altering the PEG coating, LPHNPs can be tuned over a wide pH range and this concept can be utilized to add potential functionality to the LPHNPs drug delivery toolkit.

Numerous ligands or targeted moieties improve cellular uptake via receptor-mediated endocytosis within target cells. Folic acid (FA) is widely used as a targeting ligand as it evades the attacks of drugs on normal tissues. FA binds firmly to folate receptors (FRs), which are overexpressed in several human tumors. Wu and colleagues [**70**] improve the efficiency of LPHNPs by introducing FA onto the surface of LPHNPs and forming folate-targeted lipid–polymer hybrid nanoparticles (FLPNPs). The FLPNPs comprise a PLGA core, a lecithin monolayer, a monomethoxy-poly(ethylene glycol)-S-S-hexadecyl (mPEG-S-S-C16) reduction-sensitive shell, and a covalently bound folic acid ligand. The prepared FLPNPs were used for selectively targeted delivery of doxorubicin (DOX) which suppressed human oral cavity squamous cell carcinoma (KB) cell growth and reduced the toxicity of DOX. FLPNPs showed good stability with rapid disassembly in a simulated cancer cell-reductive environment. Furthermore, an increased DOX accumulation in the solid tumor was reported in an animal tumor model by subcutaneously injecting KB cells (1 × 107 per animal) into the flank region of mice.

In another study, FA-decorated pH-sensitive LPHNPs were utilized for the co-delivery of carboplatin (CBP) and PTX for the treatment of cervical cancer [**115**]. The formed FA-CBP/PTX-LPNs showed 169.9 ± 5.6 nm particle sizes with a narrow size range of 0.151 ± 0.023. High cellular uptake (66.7 ± 3.1%) with noticeable cell inhibition capacity (23 ± 1.1%) was reported with FA-CBP/PTX-LPNs. Furthermore, FA-CBP/PTX-LPNs revealed pH-sensitive drug release and produced synergistic effects of CBP and PTX on cervical cancer.

Fucose-conjugated nanocarriers open the way for a cure for breast cancer and urge further research [**116**]. Garg et al. [**94**] utilized LPHNPs for the co-delivery of methotrexate and aceclofenac, using fucose as a target ligand against MCF-7 and MDA-MB-231 breast cancer cell lines. Prepared fucose-linked LPHNPs have a small particle size (150 nm) with good encapsulation efficiency (85–90%) and drug loading efficiency (10–12%). An improvement in bioavailability (8–10 folds) and the synergism of combinations of drugs led to superior control over tumor growth in the 7,12-dimethylbenz[a] anthracene (DMBA)-induced breast cancer mouse model.

Lipid–polysaccharide surface-modified hybrid NPs were reported by Omar et al. [**117**] using the nanoprecipitation method for the brain delivery of rivastigmine (Riv). Dextros-cholic acid (DxC) was used as a polysaccharide for the surface modification of lipid–PLGA NPs. Prepared surface-modified LPNs have a size of 111.6 ± 11.4 nm with 92 ± 1.2% an encapsulation efficiency of Riv. The in vivo investigations on albino rats demonstrated that the surface-modified LPNs penetrated the brain more efficiently and quickly than the medication solution. The surface-modified LPNs showed about a five-times higher blood–brain barrier (BBB) penetration than the drug solution. Additionally, the polysaccharide surface modification further improves brain residence time up to 40 h. These results suggested that the lipid–polysaccharide surface-modified hybrid NPs could circumvent the BBB and are predicted to reduce systemic side effects.

Monoclonal antibodies (mAbs) are also used as targeting ligands because they effectively and safely deliver drugs to desired sites; however, a limitation associated with these mAbs is their large hydrodynamic size, which may lead to a significantly increased nonspecific uptake via the reticuloendothelial system (RES) and reduce the NP circulation time. Furthermore, additional limitations of these mAbs include their nonspecific conjugation to NPs (which may result in hindered binding sites of the mAbs) and particle dimerization. The problem can be resolved through the use of small antibody variants, including minibodies, diabodies, and single-chain variable fragments (svFc). Hu et al. [**68**] synthesized anti-CEA half-antibodies (hAbs) conjugated to LPHNPs via a single-step nanoprecipitation method. The anti-CEA half-antibodies (hAbs) were produced by reducing the disulfide bonds between the heavy chains of the anti-CEA mAbs with a reducing agent. Prepared anti-CEA half-antibody (hAb)-conjugated LPHNPs were extensively characterized, and targeting abilities against pancreatic cancer cells were assayed. The results revealed that the hAb-conjugated lipid–polymer NPs showed an enhanced cancer-killing effect compared to the corresponding plain or unconjugated NPs.

Similar to mAbs, aptamer-functionalized LPHNPs are also used for the co-delivery of cytotoxic agents for treating cancer. Chen and colleagues [**118**] designed and synthesized aptamer-functionalized curcumin (CUR) and cabazitaxel (CTX)-loaded LPHNPs (APT-CUR/CTXLPNs) for the treatment of prostate cancer (PC). The A10-3.2 aptamer (5′-GGGAGGACGAUGCGGAUCA GCCAUGUUUACGUCACUCCU-spacer-NH2-3′ with 2′-fluoropyrimidines) was used in this study. The prepared APT-CUR/CTXLPNs had a mean particle size of 121.3 ± 4.2 nm and a positive surface charge of 23.5 ± 2.6 mV. APT-CUR/CTX LPHNPs showed a sustained release of CUR and CTX with an improved tumor inhibition efficiency. At a drug ratio of 2:5 (CUR:CTX), aptamer-functionalized APT-CUR/CTX LPHNPs demonstrated good cell inhibition ability, considerable tumor accumulation, and extraordinary tumor inhibition activity.

## 6. Stimuli-Responsive Drug Release from LPHNPs

LPHNPs illicit the combined release mechanisms of liposomes and polymeric NPs. Liposomes show drug diffusion and partitioning across the phospholipid bilayer toward the aqueous environment, whereas polymeric NPs exhibit surface and bulk erosion followed by drug diffusion. Further, LPHNPs can be designed for site-specific delivery in response to various stimuli like temperature, pH, redox, and magnetic fields (**Figure 6**).

**Figure 6.** Stimuli-responsive drug release approaches utilized for LPHNPs.

For instance, pH-responsive poly(β-amino ester) (PBAE) core–shell NPs coated with lipid polymers (DSPE-PEG2000, FA-DSPE-PEG2000, and lecithin) were prepared (FA/PBAE/DTX-NPs) for the target delivery of docetaxel (DTX) to breast cancer cells, i.e., 4T1 cells. The prepared NPs have uniform particle sizes and excellent physical stability. The in vitro drug release studies showed DTX release on demand at different pHs. The drug release studies at high pH (i.e., pH 7.4 and pH 6.8) showed slower release (60%) as compared to the low pH value (i.e., 90% at pH 5.5). These findings suggested that the acidic environment may stimulate the drug release behavior of FA/PBAE/DTX-NPs within tumor cells. Furthermore, the PBAE tertiary amine group enhanced the endosomal/lysosomal outflow through the proton sponge effect, and ultimately, the rapid release of DTX was observed [**119**].

Two-component reduction-sensitive LPHNPs (SLPNPs) were prepared from PCL and amphiphilic 1,2-dilauroyl-3-sn-phosphatidylethanolamine (DLPE)-methoxypolyethylene glycol (mPEG) (DLPE-S-S-mPEG) to release doxorubicin in a controlled fashion. Similarly, the other two-component insensitive LPHNPs (ILPNPs) were also prepared from PCL and DLPE-CC-mPEG as controls. The prepared SLPNPs and ILPNPs were around 100–120 nm in diameter with a spherical shape. DOX/SLPNPs and DOX/ILPNPs were both shown to be stable in water and PBS buffer (pH 7.4); however, only DOX/SLPNPs were destabilized under reductive environment, rapidly released DOX to cell nuclei, and exhibited stronger cytotoxicity against cancer cells than DOX/ILPNPs [**51**].

Photoresponsive techniques are also used to control drug release, either by triggering drug release via the photothermal effects of materials (for example, gold nanorods) or by directly shattering the drug carriers via light irradiation. To create these light-sensitive nanocarriers, the structure should include photochromic groups whose photoreaction might increase polarity and

shift the hydrophilic–hydrophobic balance sufficiently to rupture the nanostructure when exposed to light. Yao and colleagues [**120**] reported a photo-responsive LPHNPs system having a doxorubicin-encapsulated PLGA core coated with a lecithin outer monolayer as an interface and a photo-sensitive layer of a PEG-hexadecyl block polymer with a 2-nitrobenzyl linker with anti-biofouling properties. The photoresponsive polymeric shell triggers drug release under light sensitization. In vitro results showed that the prepared LPHNPs showed excellent light-triggered drug release (76% release with light irradiation versus only 10% release without light irradiation). The confocal microscopy and flow cytometry results also confirmed the light-controlled drug-release behavior of the LPHNs within the cancer cells.

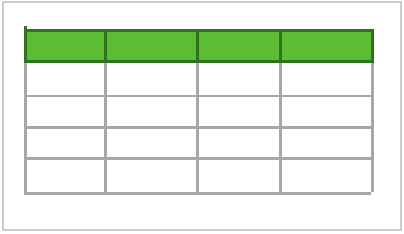
Redox-responsive LPHNPs are typically intended to release their payload at the tumor site where the concentration of glutathione (GSH) is higher. Wang and colleagues [**121**] prepared and reported afatinib-loaded, redox-sensitive, Tf-modified LPHNPs (Tf-SS-Afa-LPNs) for selective delivery to lung cancer. The prepared Tf-SS-Afa-LPNs were spherical in shape with a 103.5 ± 4.1 nm particle size and −21.2 ± 2.4 mV zeta potential. The in vitro drug release studies showed an increased afatinib release from 25% to 80% with increasing GSH concentrations from 0.1 to 10 mM, respectively.

Stimuli-responsive drug release by using external magnetic fields is another fascinating technique. Joshy and colleagues [**122**] prepared and reported NiFe2O4 NPs (NFO)-reinforced LPHNPs (NLPNs) based on the biodegradable polymer PVA/SA encapsulating zidovudine (AZT). Under the influence of magnetic fields, 80% of the AZT was released and only 13% was released without being subjected to magnetic fields after 48 h due to the presence of magnetic NPs (NFO).

## 7. Patents on LPHNPs

LPHNPs have attracted significant attention owing to their several advantages compared to lipid or polymer NPs. Henceforth, numerous researchers are focusing on translating their research results and are applying to acquire the intellectual property rights. **Table 3** presents recently granted patents on LPHNPs.

**Table 3.** List of patents granted on LPHNPs for therapeutic applications.





## 8. Conclusions and Future Perspective

LPHNPs have been reported as a promising nanocarrier class, offering the pharmaceutical benefits and physicochemical characteristics of both polymeric NPs and liposomes. LPHNPs, exhibiting enhanced stability, preventing drug leakage, possessing easy surface functionalization possibilities, and targeting ability, have proven to be profligate carriers, advancing current nanotherapeutics. The surface functionalization of LPHNPs prolongs the blood circulation time, enhances the target specificity, and improves their physicochemical properties as well as their cell associations such as cellular membrane permeability and immune responses. LPHNPs have been reported to successfully deliver siRNA and small molecules individually for cancer therapy while minimizing the toxicity associated with anticancer therapeutics. Although extensive research has been performed in LPHNPs, researchers are advised to focus on exploring the potentially unexplored areas and use the advancements in LPHNPs design to advance the current therapeutics in pharmaceutics. The selection of proper lipid and polymer combinations in the preparation of LPHNPs may improve their performance and long-term stability. Storage stability is another important parameter and decisive factor for their transition from bench to bedside, but it has not yet been established. Furthermore, a global initiative involving researchers, industrial professionals, and the FDA is necessary to address difficulties, bridge the gap, and overcome different impediments to the clinical translation of LPHNPs. To expand the number of products flowing from academic labs to the market, both industry and academia will need to move toward each other and collaborate while keeping regulator expectations in mind.

## Author Contributions

Conceptualization, S.J. and K.K.B.; formal analysis, P.K. and J.V.; resources, M.K. and J.M.R.; writing—original draft preparation, A.V., J.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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## Data Availability Statement

Not applicable.

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## Conflicts of Interest

The authors declare no conflict of interest.

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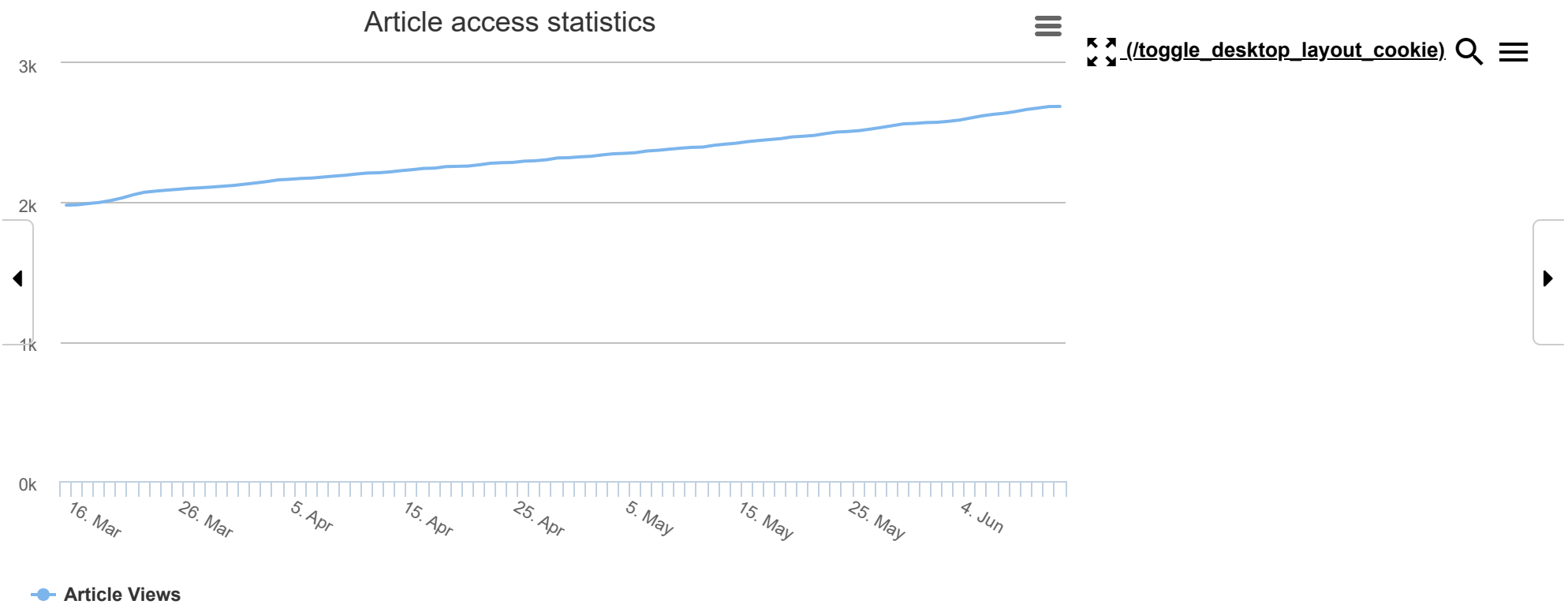
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# Comprehensive review on pharmacological effects and mechanism of actions of taxifolin: A bioactive flavonoid

Shweta Jain [a], Ankur Vaidya [b]

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## Highlights

- Taxifolin (TAX) a flavanonol plagiaristic of flavonoids is a dihydroquercetin derivative.
- TAX possesses numerous pharmacological activities and recommended for the variety of disease.

- TAX also inhibits a number of enzymes, including, tyrosinase, angiotensin converting enzyme (ACE), diacylglycerol acyltransferase (DGAT) and microsomal triglyceride transfer protein (MTP), etc.
- Moreover, many nanoparticles of TAX provide improved bioavailability, sustained release and better antioxidant activity.


## Abstract

### Introduction

Uses of flavonoids have been increased tremendously in the past few years to offer prevention, relief, and to cure a variety of diseases. Taxifolin (TAX), a flavonoid, belong to subcategory flavanone is a dihydroquercetin, possesses numerous pharmacological activities.

### Methods

An extensive literature survey utilizing electronic database such as Google Scholar, Pubmed and Scopus up to 2022 was performed to obtain the sources and chemical structure of TAX. The search data were explored to conclude the pharmacological activity and mechanism of action of TAX.

### Results

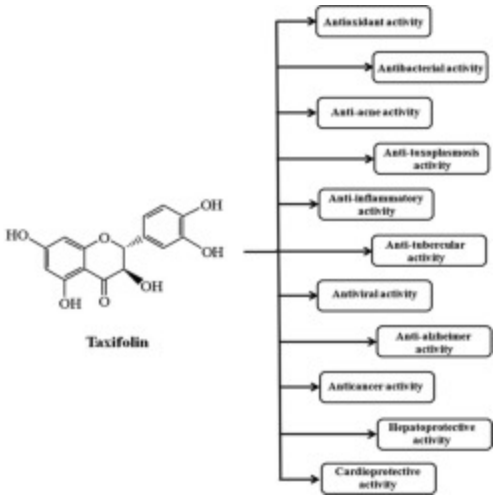
TAX occurs naturally in citrus fruits, onion, and many other plants including Siberian larch, Pseudotsuga taxifolia, Taxus chinensis var. mairei and Pinus roxburghii as well as marketed under the trade name of Venoruton®, Legalon™ and Pycnogenol™. Numerous studies have been reported to confirm pharmacological activities of TAX. Studies scientifically proven the beneficial effects of TAX against variety of diseases and recommended for the treatment of bacterial infection (including acne and toxoplasmosis), cardiovascular diseases, inflammation, cancer diseases, viral infections, Alzheimer, diabetes, allergic reaction, immunodeficiency etc. TAX also inhibits several enzymes, including, tyrosinase, angiotensin

converting enzyme (ACE), diacylglycerol acyltransferase (DGAT), microsomal triglyceride transfer protein (MTP), and so forth. Moreover, nanoparticle formulations of TAX provide improved bioavailability, sustained release and better antioxidant activity.

## Conclusion

The present review describes numerous biological and enzymatic activity of TAX and also explores the functional features of TAX responsible for these activities.

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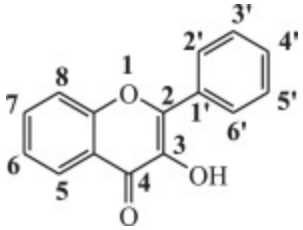
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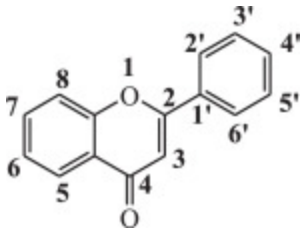
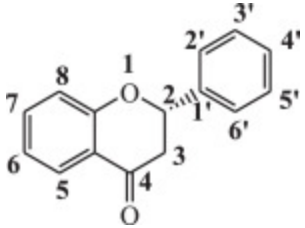
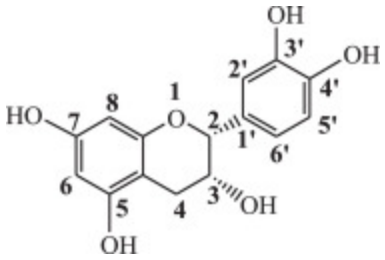
## 1. Introduction

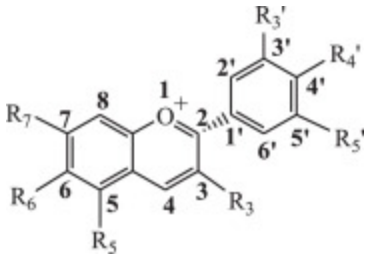
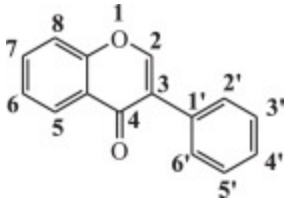
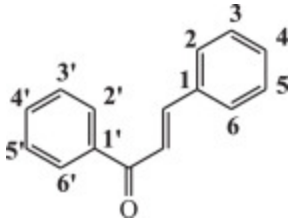
Flavonoids are widely distributed secondary metabolites, having low molecular weight hydroxylated phenolic substances [1,2]. Flavonoids are the plant-derived polyphenols, which are most traditional Chinese medicine and possess remarkable properties [3]. Generally, flavonoids occur in plants as aglycones, glycosides or methylated derivatives and impart different color shades (blue, scarlet and orange) in leaves, flowers and fruits [4,5]. Flavonoids exhibits broad range of health-promoting and disease-preventing effects [6], [7], [8]. Flavonoids showed beneficial effects in the treatment of numbers of diseases, including cancer, Alzheimer's, atherosclerosis, etc. Flavonoids coupled with their antioxidant property as free-radical neutralizers and modulate key cellular enzymes [9], [10], [11], [12]. Consumption of red wine or dietary flavonoids decreases the rate of cardiovascular mortality [13].

Flavonoids are mainly classified into flavonols, flavones, flavanones, flavanols, anthocyanidins, isoflavone and chalcones. Each category has their distinct examples, are summarized in Table 1.

Table 1. Varieties of flavonoids with their suitable examples.

| | Types of Flavonoids | Examples |
|---|---|---|
| FLAVONOIDS | Flavonols  | Galangin: 5,7=OH<br>Kaempferol: 5,7,4′=OH<br>Fisetin: 7,3′,4′=OH<br>Morin: 5,7,2′,4′=OH<br>Quercetin: 5,7,3′,4′=OH<br>Myricetin: 5,7,3′,4′,5′=OH |

| Types of Flavonoids | Examples |
|---|---|
| Flavones  | Chrysin: 5,7=OH<br>Baicalein: 5,6,7=OH<br>Apigenin: 5,7,4′=OH<br>Luteolin: 5,7,3′,4′=OH<br>Acacetin: 5,7=OH; 4′=$OCH_3$<br>Diosmetin: 5,7,3′=OH; 4′=$OCH_3$ |
| Flavanones  | Naringenin: 5,7,4′=OH<br>Eriodyctiol: 5,7,3′,4′=OH<br>Hesperetin: 5,7,3′=OH; 4′=$OCH_3$<br>Homoeriodyctiol: 5,7,4′=OH; 3′=$OCH_3$<br>Taxifolin: 3,5,7,4′,5′=OH |
| Flavanols  | Epicatechin: 5,7,3′,4′=OH |

| Types of Flavonoids | Examples |
|---|---|
| Anthocyanidins  | Cyanidine: 5,7,3′,4′=OH; 6,5′=H |
| Isoflavones  | Daidzein: 7,4′=OH<br>Genistein: 5,7,4′=OH<br>Biochanin A: 5,7=OH; 4′=$OCH_3$ |
| Chalcones  | Xanthohumol: 4,2′,4′=OH; 6′=$OCH_3$; 3′=Prenyl |

In traditional Chinese herbal medicine, fructus polygoni orientalis (FPO) is the dried and mature fruit of Polygonum orientale L, which has been widely used in China for the treatment of numerous diseases. Taxifolin (TAX) (5,7,3′,4′-flavanonol or dihydroquercetin), is one of the most abundant flavonoids in FPO has been listed as an indicator of quality for FPO in the Chinese Pharmacopeia 2015 edition [14,15].

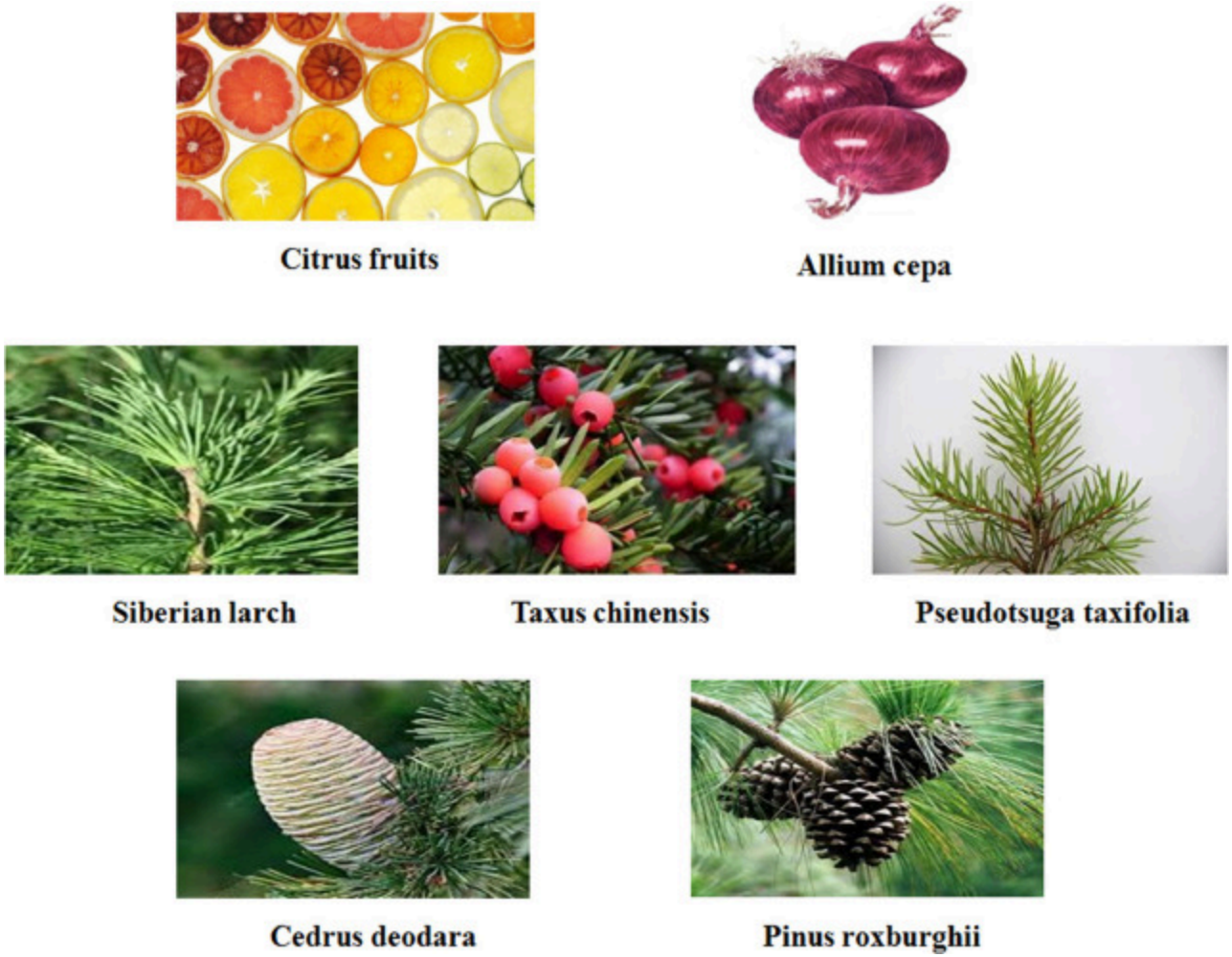
TAX is a potent antioxidant as well as a common bioactive component of dietary supplements and many herbal formulations including Legalon™, Pycnogenol® and Venoruton® contains TAX. Compared to other antioxidant flavonoids, TAX exhibits superior activity as a chemopreventive agent [16,17].

TAX inhibited the formation of free radicals via both reactions, i.e. by inhibiting the cytochrome c-Cardiolipin complex, and chain lipid peroxidation, resulting in cytochrome c release from mitochondria and apoptosis inhibitory potential [18]. TAX also enhances the efficacy of ceftazidime and levofloxacin in the treatment of methicillin-resistant S. aureus infected patients admitted in Kunming General Hospital, Kunming, China [19]. Nowadays TAX is alternative for numerous diseases, including Alzheimer's, cardiovascular, diabetes, tumour and inflammation [20].

An exhaustive literature was studied for the present study. Total 636 papers were screened for herbal medicine including flavonoids, out of which only 96 papers were selected on the basis of sources, chemistry, mechanism of action and pharmacological effects of TAX via the following databases: Embase, Google, MEDLINE, PubMed, Scopus, and Web of Science. The search terms included: traditional Chinese medicine, Chinese preparation, flavonoids, sources of TAX, chemistry of TAX, pharmacological effects of TAX, antioxidant or free radical scavenging activities of TAX, antibacterial or antimicrobial activities of TAX, anti-acne or tyrosinase inhibition of TAX, anti-toxoplasmosis activity of TAX, anti-inflammatory activity of TAX, anti-tubercular activity of TAX, antiviral activity of TAX, anticancer activity of TAX, anti-alzheimer activity of TAX, hepatoprotective activity of TAX, cardioprotective activity of TAX, effects of TAX on osteoclastogenesis, diacylglycerol acyltransferase (DGAT) or microsomal triglyceride transferprotein (MTP) inhibitory activity of TAX, and nanoformulations of TAX.

## 2. Sources and chemistry of TAX

TAX was first isolated from Pseudotsuga taxifolia (Douglas fir bark) and latterly also isolated from Larix gmelini and Larix sibirica (Dahurian and Siberian larch). TAX received the considerable attention and found in citrus fruits, as well as in variety of plants including Taxus chinensis var. mairei, Cedrus deodara and Pinus roxburghii (Fig. 1). It is also commonly found in onions (Allium cepa) and in milk thistle (Silybum marianum) [21].



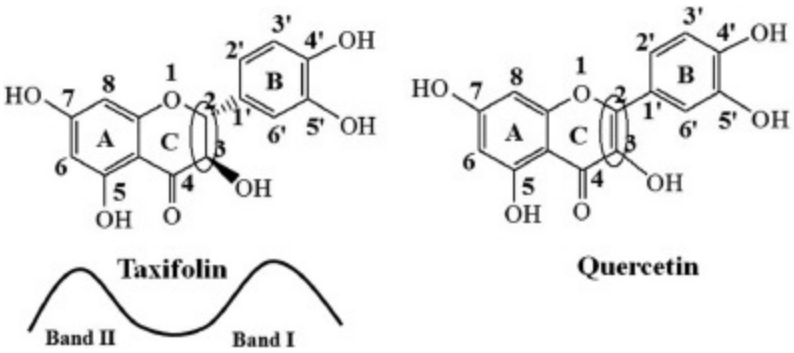

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Fig. 1. Numerous plant sources of TAX: Citrus fruits, Allium cepa, Siberian larch, Taxus chinesis, Pseudotsuga taxifolia, Cedrus deodara, Pinus roxburghii.

TAX is a pentahydroxyflavanone and commonly known as dihydroquercetin. TAX is a 2,3-dihydro derivative of quercetin i.e., devoid of $C_2$—$C_3$-double bond in the ring-C as compared to quercetin. The presence of 3′,4′-O-dihydroxyl group in the B-

ring, and 4-keto group in the C-ring of TAX liable for extreme radical scavenging mediated antioxidant activity, while the O-dihydroxy structure in the B ring conferring stability [22]. Due to lack of 2,3-double bond in conjunction with the 4-oxo function in the C-ring makes it less potent antioxidant as compared to other flavonoids i.e., quercetin (Fig.2) [23]. Jaganath et al. [24] investigation claimed the intestinal metabolism of quercetin to TAX and afterward to alphitonin, inside the human gut by the action of bacteria Eubacterium ramulus.




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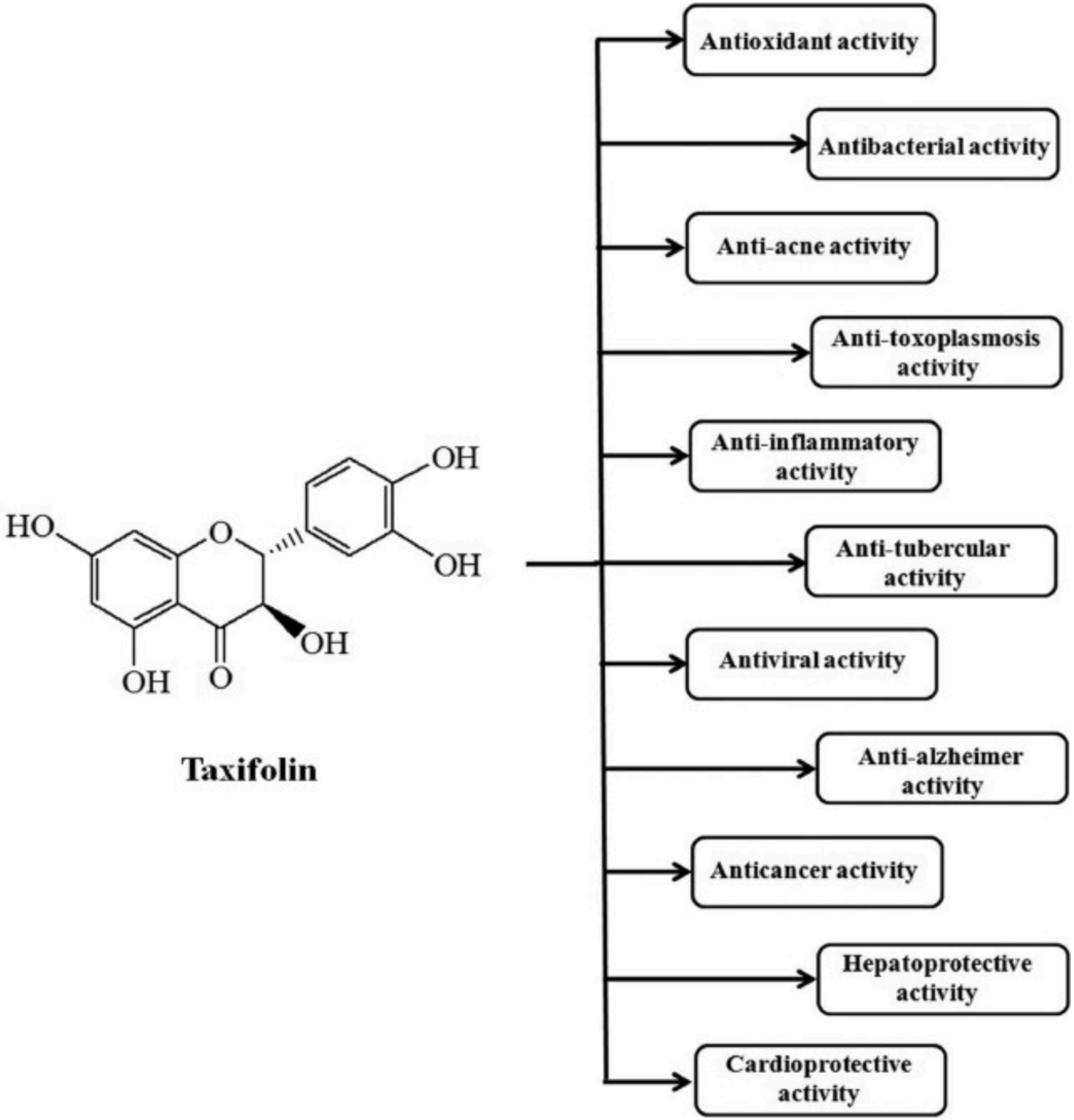
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Fig. 2. Structure of Taxifiolin (TAX) and Quercetin, representing Band I and Band II absorption region.

The IUPAC name of TAX is (2R, 3R)−2-(3,4-Dihydroxyphenyl)−3,5,7-trihydroxy-2,3-dihydrochromen-4-one [21]. TAX ($C_{15}H_{12}O_7$) occurs as a yellow colour crystalline powder, having molecular weight 304.25 g/mol. It melts at the temperature between 218 and 253 °C as well as showed base peak $(M+H)^+$ at m/z value 305.068 [25]. The ultraviolet (UV)-absorption spectrum of TAX in spectroscopic exhibits two bands corresponding to B ring absorption (i.e., Band I of 320–385 nm) and for A ring absorption (i.e., Band II of 250–285 nm) [26].Both trans and cis forms of TAX are soluble in polar solvents including water-alcohol solutions [27].

## 3. Pharmacological effects of TAX

The pharmacological effects of TAX are summarized in Fig.3.




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Fig. 3. Numerous pharmacological activities of TAX: Antioxidant activity, Antibacterial activity, Anti-acne activity, Anti-toxoplasmosis activity, Anti-inflammatory activity, Anti-tubercular activity, Antiviral activity, Anti-alzheimer activity, Anticancer activity, Hepatoprotective activity and Cardioprotective activity etc.

## 3.1. Antioxidant effects

TAX is one of the most abundant dihydroflavonols and acts as antioxidant-rich functional food. Due to antioxidant/antiradical activity, including reactive oxygen species (ROS) scavenging and metal-binding activities of TAX, it has been endorsed for cardiovascular disease, skin disease, cognitive feature, allergic reactions, etc. [28].

Chinese research group Zhou and colleagues [29] identified TAX (92.07%) as flavonoids in the extract of L. olgensis var. using high performance liquid chromatography-mass spectrometry/ mass spectrometry (HPLC-MS/MS). The obtained TAX exhibited strong antioxidant activity, surpassing that of butylated hydroxytoluene (BHT).

The antioxidants and antiradical activities of TAX showed $IC_{50}$ values 9.91 g/ml, 231.04 g/ml, 0.83 g/ml, 77 g/ml, 36.41 g/ml and 81.02 g/ml for different *in vitro* methods viz. Superoxide radicals ($O_2^{\bullet -}$), N,N-dimethyl-p-phenylenediamine radical-scavenging ($DMPD^{\bullet +}$-scavenging), 2,2′-azino-bis (3-ethylbenzo-thiazoline-6-sulfonic acid) radical-scavenging (ABTS+•-scavenging), 1,1-diphenyl-2-picryl-hydrazl radical-scavenging (DPPH•-scavenging), $Fe^{+}$-chelating activities and inhibition of lipid peroxidation as compared to standard butylated hydroxyanisole (BHA) $IC_{50}$ i.e. 34.65 g/ml, 231.01 g/ml, 12.30 g/ml, 86.63 g/ml, 30.13 g/ml and 90.12 g/ml, respectively. Based on structure-activity relationship, authors proved that antioxidant/ antiradical activity depends on steric freedom and the presence of -OH groups. Both, an increase in number of -OH and especially at the para position of the aromatic ring increase the activity [14].

Additionally, Chinese research group Li and colleagues [30], reported the significant antioxidant activity ($IC_{50}$ values 259.2 µg/ml, 663.9 µg/ml, 16 µg/ml, 4.6 µg/ml, 22.4 µg/ml and 33.7 µg/ml) of TAX against various free radicals/reactive oxygen species (ROS) viz. $OH^{\bullet}$, 2-phenyl-4,4,5,5-tetramethylimidazoline-1-oxyl-3-oxideradical-scavenging (PTIO•-scavenging), $DPPH^{\bullet}$, $ABTS^{+\bullet}$-scavenging, $Fe^{3+}$-reducing and $Cu^{2+}$-reducing assays as compared to trolox ($IC_{50}$ values 411.4 µg/ml, 736.8, 18.5 µg/ml, 11.4 µg/ml, 40.4 µg/ml and 62.8 µg/ml, respectively). The same Chinese authors further proved direct TAX protects

mesenchymal stem cells derived by bone marrow from Fenton reagent through its direct $OH^{\bullet}$ $DPPH^{\bullet}$, $ABTS^{+\bullet}$-radical scavenging activity and indirect increases $Cu^{2+}$ and $Fe^{3+}$ reducing levels. In another study, treatment with the TAX (5–50μM) reduces hypertrophy, ROS generation and protein synthesis induced by angiotensin II in cardiomyocytes [31].

Another study reported that TAX showed strong antioxidant/free radical scavenging activity against various free radicals viz. $DPPH^{\bullet}$, $ABTS^{\bullet}$, FRAP and $OH^{\bullet}$ radical with $IC_{50}$ values 16.48μg/ml, 66.34μg/ml, 18.17μg/ml and 11.42μg/ml, respectively. Study results proved that at unit concentration of TAX exhibited a strong protective effect on pUC19 plasmid DNA from $OH^{\bullet}$ radical-induced damage. Treatment with TAX exhibited protective effects on zebrafish embryos (Danio rerio) against cadmium-induced toxicity, which is characterized by increase survival, increases hatching, decreases phenotypic abnormalities, decreases heart rate, reducing lipid peroxidation and increase antioxidant enzyme level [32].

## 3.2. Antibacterial activity

Since ancient age, flavonoids have been recommended for bacterial infection. Numbers of isolated flavonoids including apigenin, baicalin, chrysin, luteolin, myricetin, quercetin and rutin etc. have been reported till date for their potential role as anti-infective agents [33].

Hydroalcoholic extracts of pterospartum tridentatum contains TAX and other polyphenols, displayed robust antibacterial activity against both methicillin sensitive and methicillin-resistant Staphylococcus aureus. The antibacterial activity of Pterospartum tridentatum, related to the synergistic effects of TAX (flavonols) with other flavones or isoflavones compounds present in the extract [34].

TAX isolated from the kempas (Koompassia malaccensis) extracts showed significant antibacterial activity against Streptococcus sobrinus ($IC_{50}$, 21.8) as well as glucosyltransferase inhibitory activity ($IC_{50}$,53g/ml). The antibacterial activity of TAX might be due to the presence of 3′,4′-dihydroxyl groups which may further increase on dihydroxylation at the 5-position and 7-position. The authors recommended the use of TAX as a natural anti-cariogenic agent for the treatment of dental caries [35]. Treatment with 6-(p-hydroxy benzyl)-TAX-7-O-β-D-glucoside significantly reduced (52–80%) the growth of all four tested bacterial species viz. Azospirillium lipoferum, Bacillus sp, Escherichia coli and Lactobacillus sp. [36].

## 3.3. Anti-acne and tyrosinase inhibition effect

Usually, compounds or materials possessing antioxidant, anti-lipase, anti-bacterial and anti-inflammatory activities have anti-acne activity [37,38]. Dej-adisai et al. [39] reported the tyrosinase inhibition potential (90.57%) and antimicrobial activity of Artocarpus integer root extract.

Compounds with anti-acne efficacy against Propionibacterium acnes as well as with tyrosinase inhibition activity acts as a potent inhibitor of pro-inflammatory lipids in sebum in addition to reduce post-acne scar formation. Batubara et al. [40] evaluated the TAX and other flavanonol rhamnosides isolated from the bark of Kempas i.e. Koompassia malaccensis, for its anti-acne efficacy by determining its antimicrobial efficacy against P. acnes, P. acnes lipase inhibition, and antioxidant activity as well as tyrosinase inhibition activity. Study results demonstrated that no remarkable antimicrobial activity was observed in all compounds against P. acnes while good lipase inhibition property and antioxidant activity was shown by TAX (31.16% inhibition 10 μg/ml concentration). However, TAX, showed 24.12% and 5.18% inhibition of L-tyrosine and levodopa (L-DOPA) in inhibition of tyrosinase activity.

## 3.4. Anti-toxoplasmosis activity

Toxoplasmosis is a serious form of the disease, occurs mostly in immunocompromised females/ or during pregnancy and passes it on to the foetus, caused by Toxoplasma gondii. Sulfadiazine, pyrimethamine, and the combination of pyrimethamine-sulfadiazine or clindamycin-atovaquone are prescribed for treatment of toxoplasmosis [41].

Previously reported research claim the anti-toxoplasmosis activity of flavonoids including luteolin, naringenin, quercetin and TAX. Both quercetin and luteolin reported for anti-toxoplasmagondii activity [42].

Abugri et al. [43] investigated the anti-toxoplasmagondii activities of TAX and pyrimethamine alone and in combination by colorimetric 3-(4, 5-dimethylthiazol-zyl)−5-(3-carboxymethoxyphenyl)−2-(−4-sulfophenyl)−2H- tetrazoliuzolium, (MTS) assay on T. gondii RH strain, Human foreskin fibroblast (HFF) and Hek-293 cells. Study results revealed that at low concentration, treatment with pyrimethamine ($IC_{50}$ 0.84 μg/ml) followed by combination of TAX with pyrimethamine ($IC_{50}$ 1.39 μg/ml) significantly ($p<0.5$) inhibited the growth of Toxoplasma gondii parasites with low cytotoxicity to the infected cell lines. The anti-toxoplasmagondii activity of TAX was owing to inhibition of calcium-dependent protein kinase activity in Toxoplasma gondii. The finding of the above research suggested the combination of TAX with pyrimethamine may be a

promising tool for toxoplasmosis treatment. Nevertheless, more studies were proposed to determine their safety and efficacy.

## 3.5. Anti-inflammatory activity

TAX isolated from plant Madhuca butyracea was evaluated for anti-inflammatory activity *in vivo*. TAX (40 mg/kg b.w. i.p) exhibited significant ($p<0.001$) anti-inflammatory activity (44.2%) as compared to hydrocortisone (10 mg/kg b.w., i.p.) (44.2%). The ratio of lethal dose50 to effective dose50 ($LD_{50}/ED_{50}$) for TAX was 12.2 as compared to 11.6 for hydrocortisone. Although, therapeutic index of TAX was found to be equal to hydrocortisone, yet TAX was less potent (one-eighth) as hydrocortisone on the carrageenan-induced oedema. Anti-inflammatory effects of TAX were due to decrease in the elevated level of serum aminotransferase activity or increase in the enzyme ATP phosphohydrolase activity [44]. In another study, TAX isolated from the leaf extract of Opuntia humifusa inhibited lipopolysaccharide (LPS)-induced tumor necrosis factor (TNF)-α and interleukin (IL)−6 production in cytokine assay and cyclooxygenase-2 expression in western blot analysis, which indicated it's promising (significant, $p<0.05$) anti-inflammatory effects [45].

Very recently, Chinese researchers investigated the protective effects and mechanisms of TAX against inflammatory reaction in RAW264.7 cells induced by lipopolysaccharide (LPS). The results revealed that TAX improved the inflammatory responses via involving the phosphorylation expression level of mitogen-activated protein kinase (MAPK) signal pathway [46].

## 3.6. Anti-tubercular activity

DNA gyrase and aminoacyl-tRNA synthetases are the primary targets for novel anti-tubercular agents. Keeping these properties in mind Davis et al. [47], identified novel anti-tubercular (anti-TB) agent by virtually screening a group of eight flavonoids, including afzelechin, aromadendrin, 4′-hydroxy wogonin, 4′−7-isoflavandiol (equol), licoflavone C, 3-O-methyl quercetin, sigmoidin A and TAX, against the crystal structure of DNA gyrase and isoleucyl-tRNA synthetase (IleRS). TAX had shown highest interactions at the active site of amino acids (i.e. Asn46, Arg76, Ile78, Pro79, Gly101, Lys103 and Thr165) as compared to other flavonoids in docking studies. Furthermore, anti-TB activity of TAX was tested, which showed comparable ($IC_{50}\leq$ 12.5 μg/ml) activity as standard drugs pyrazinamide, ciprofloxacin, and streptomycin ($IC_{50}\leq$ 3.125, $IC_{50}\leq$ 3.125 and $IC_{50}\leq$ 6.25 respectively).

## 3.7. Antiviral activity

TAX also shows antiviral activities through inhibition of viral particle attachments through glycosaminoglycans (GAG) or replication process or viral genome synthesis [48].

Efficacy of TAX against the cell culture adapted hepatitis A virus (HAV) strain CF 53 was assayed by Biziagos et al. [49]. Study results proved that the treatment with TAX for 15 days showed concentration-dependent reductions in both the infectivity and antigenicity of HAV and shown 0.77 $\log_{10}$ viral titer reduction value at 59 μg/ml concentrations of TAX.

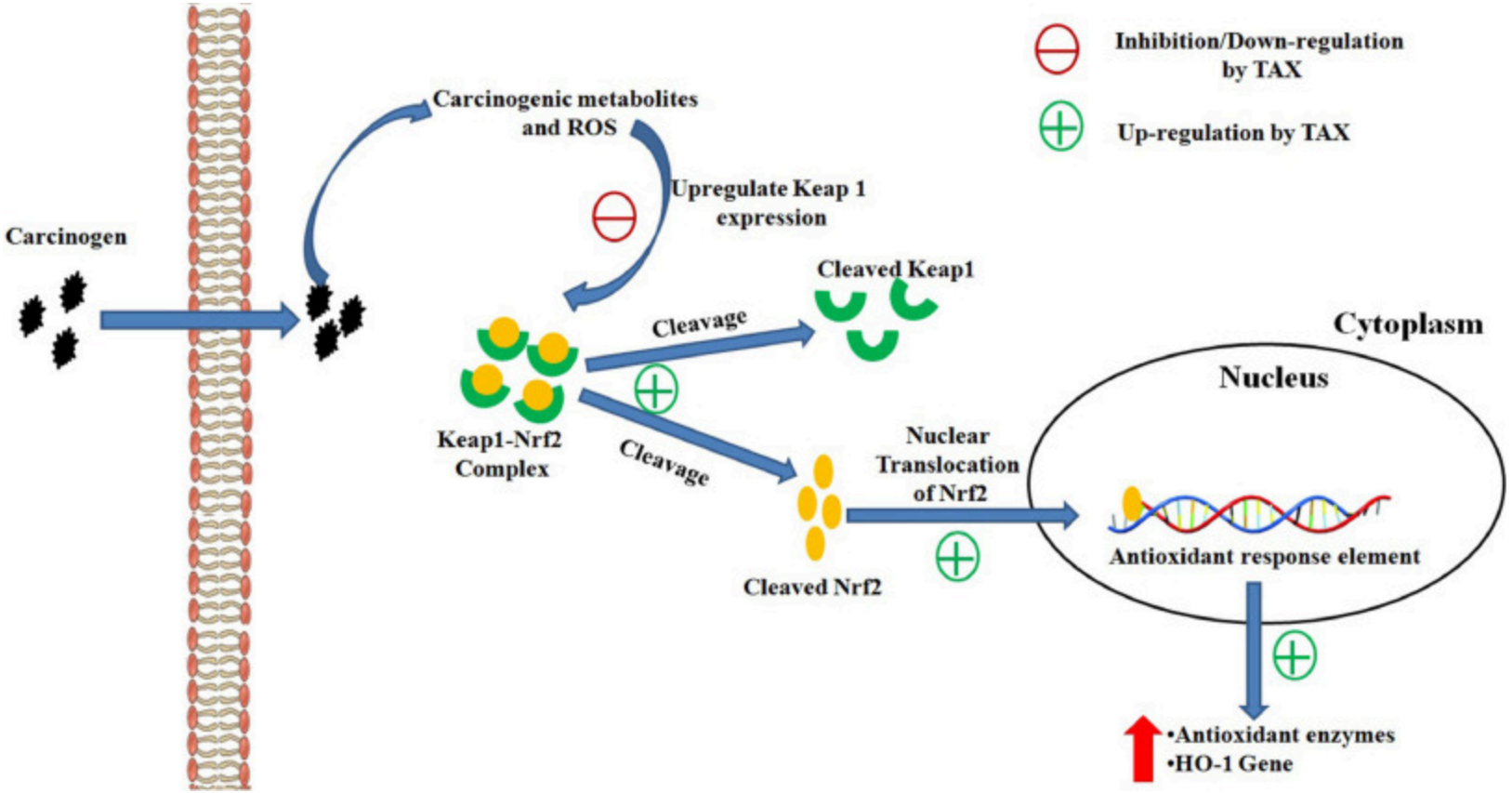
## 3.8. Anticancer activity

The consumption of flavonoids rich food products reduces the risk of cancers. Although the cancer-protective mechanisms of flavonoids are still unclear, however researchers believe that the fatty acid synthase (FAS) inhibitory properties may be responsible for apoptosis induction in cancerous cells [50].

TAX has been reported as a potent chemotherapeutic agent, showed brawny antiproliferative effects against different cancer cells. TAX inhibits fatty acid synthase in cancer cells and prevents the growth and spread of cancer cells [51]. TAX stimulated nuclear factor E2-related factor 2 (Nrf2)-dependent expression of phase II detoxifying and antioxidant enzymes. Notably, TAX also augments nuclear heme oxygenase-1 (HO-1) expression in cytoplasm and nuclear translocation by inducing Nrf2 expression. TAX also regulates genes and inhibited ovarian cancer cell mitosis [52], and causes prostate cancer cell apoptosis [53].

Kuang et al. [15] a Chinese investigator, investigated TAX effects on Nrf2 in JB6 P+ cells (skin keratinocyte cell line). Results revealed up-regulated mRNA and protein levels of Nrf2 and its downstream genes HO-1 and NAD(P)H quinone oxidoreductase 1 (NQO1). TAX also inhibited 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced colony formation and induced antioxidant response element (ARE)-luciferase activity. Furthermore, TAX also inhibited the expression levels of histone deacetylase (HDAC) and DNA methyltransferase (DNMT) proteins in the western blotting study. Study results strongly recommended that TAX induced Nrf2 mediated epigenetic pathway for the treatment of skin cancer. Furthermore, the authors suggested that TAX alters DNA demethylation and epigenetically enhances Nrf2 expression of anti-oxidative stress pathway, thereby contributes to prevent the neoplasm growth in JB6 $P^+$ cells.

In other study, TAX showed high binding affinity towards Kelch-like ECH-associated protein 1 (Keap-1) and HO-1 and down-regulate Keap-1 and up-regulated the expressions of protective Nrf-2 and associated HO-1 and NQO1 proteins. Study results proved that TAX exhibits its protective effect due to its antioxidant effects viz. inhibits lipid peroxidation, increase enzymatic and decreases non-enzymatic anti-oxidative markers and showed up-regulation of protective HO-1, NQO1, and Nrf-2 expressions, following suppression in the Keap-1 mRNA expression (Fig.4) [54].




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Fig. 4. Schematic representation of Nrf-2-Keap-1-HO-1 and antioxidant pathway mediated anticancer mechanism of TAX.

Furthermore, treatment with TAX decreased expression of Wnt/β-catenin gene, AKT gene, surviving gene and protein, thereby induces apoptosis and cell cycle arrest in G2 phase in both i.e., colorectal cancer cell lines (HCT116 and HT29) and HCT116 xenograft model, and ultimately produces protective effects against colon cancer [20].

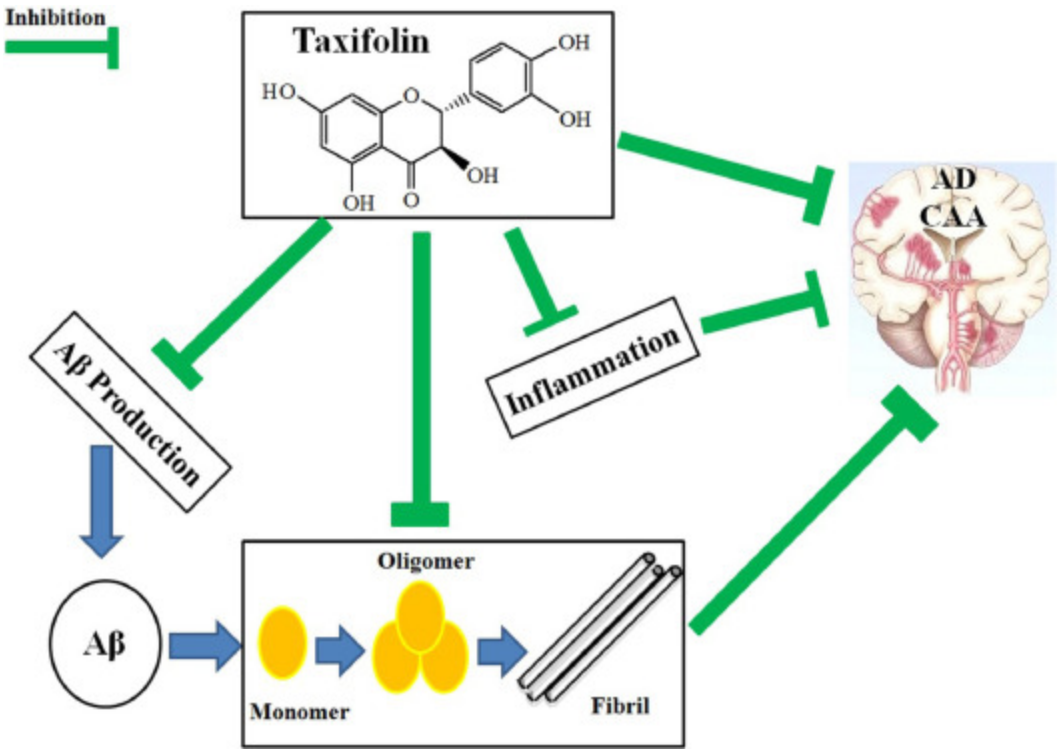
Manigandan et al. [55] also reported chemopreventive activity of TAX. TAX (4μg/kg bw, op) induced antioxidant mediated apoptosis and caused histological alterations of cancer cells. Furthermore, TAX increased DNA fragmentation and regulates cell proliferation. As compared to 5-FU, TAX more significantly reduced occurrence of colon cancer.

Andrographolide (Andro) a diterpenoid lactone has recently been introduced by Chinese researchers as novel anticancer agent displaying induction of apoptosis and or G2/M arrest in cancer cells. Study revealed anticancer potential of Andro against varieties of cancer cell [56]. The delivery of Andro alone or in combination with other cytotoxic agents, including flavonoids may be effective for cancer therapy [57]. Zhang and colleagues [58] a group of Chines scientist, revealed the significant improved anti-cancer activity of Andro in TAX combination, by distracting microtubule dynamics and triggering the spindle assembly checkpoint (SAC).

Alzaharna et al. [59] studies revealed the synergistic effects of TAX with Andro in HeLa cells. The TAX combination attenuating ROS and autophagy, increasing mitochondrial membrane potential (MMP) loss, the release of apoptosis-inducing factor (AIF) and cytochrome-c and ultimately cell death. This result was the first evidence that TAX induce cytotoxic effect of Andro.

## 3.9. Anti-Alzheimer activity

Alzheimer disease (AD) is characterized by instinctively aggregation and plaque formation by amyloid-β (Aβ) peptide. Aggregation of soluble Aβ oligomeric peptide (Aβ42) leads to the pathogenesis of AD [60,61]. TAX contribute to preventing and/or treating Aβ-associated cognitive dysfunction, including cerebral amyloid angiopathy (CAA) and AD (Fig.5) [62].




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Fig. 5. TAX prevent and/or treating Aβ-associated cognitive dysfunction including AD and CAA.

A docking study reported by Keshet et al. [63] showed the participation of Lys28 and the C-terminal region in the binding with myricetin for Aβ interaction with flavonoids.

Silymarin obtained from Silybum marianum, improved behavioral abnormalities in AD by attenuating amyloid-β plaque burden [64].

Sato et al. [65] reported the structure-activity relationship (SAR) studies of TAX, which revealed that 3,4-dihydroxyl groups present on B-ring of TAX was critical for anti-aggregative ability against 42-residue amyloid-β protein (Fig.2). The same research group further reported that (+)-TAX, in the presence of sodium periodate (an oxidant), leads to the formation of

Aβ42-TAX adduct thereby prevents Aβ42 aggregation/pathogenesis of AD. Unlike curcumin (non-catechol-type flavonoid), (+)-TAX does not interact with β-sheet region in Aβ42. This study proved that (+)-TAX specifically suppresses Aβ42 aggregation in the elongation phase by targeting Lys-residues ($Lys^{16}$and/or $Lys^{28}$) and strongly suggested as a worthy candidate for AD therapeutics [66].

## 3.10. Hepatoprotective activity

Oxidative stress caused by overloading antioxidant capacity on cells, is the primary root of liver disease. Numerous natural and synthetic antioxidants have been utilized for the treatment of liver diseases. Flavonoids possess antioxidative properties also show hepatoprotective activities [67].

Polyak et al. [68] tested the effects of silymarin and its pure constituents including TAX in hepatoprotective assays. Except isosilybin B, all compounds were well tolerated by Huh7 human hepatoma cells up to 80 μM. Silymarin and its derived compounds including TAX showed strong hepatoprotective activity in all assays tested except in T cell proliferation. This study suggested that silymarin and its pure constituents are effective against hepatitis C virus (HCV) in some patients, however the dose of silymarin and its derivatives need to be standardize.

Akinmoladun et al. [69] reported the protective effect of TAX and other flavonoids. Catechin, quercetin and TAX showed significant hepatoprotective activity ($p<0.0001$). However, quercetin showed top apparent ameliorative activity over catechin and TAX, but TAX showed improved hepatoprotective activity compared to catechin and similar to quercetin. This study demonstrate significant correction of hepatic dysfunction by flavonoids particularly by TAX and quercetin over the catechin. Chen et al. [70] reported the hepatoprotective activity of TAX via its immunosuppressive effects on concanavalin A (Con A)-treated mice model. A significant decreased in serum level of alanine transaminase and aspartate transaminase was reported *in vivo* after-tax administration. Additionally, down-regulation of Perforin, Granzyme B, chemokine, apoptosis factors, pro-inflammatory cytokines, transcription factors and inducible nitric oxide synthase (iNOS) were also reported. Zhao et al. [71] reported that TAX can inhibit autoimmune hepatitis. Chen et al. [72] demonstrated caring effects of TAX on acute liver injury in the aspects of antioxidant, anti-inflammatory activity, and inhibition of hepatocyte apoptosis. However, further studies were proposed by same research group to determine the TAX mediated hepato-protective mechanism.

## 3.11. Cardioprotective activity

Flavonoids reduce the oxidative stress in vessels and thus show cardioprotective effects [73,74]. Arutyunyan et al. [75] determined the *in vivo* inhibitory effects of TAX on the angiotensin converting enzyme (ACE) as well as on the formation of ROS/RNS. Study results demonstrated that the treatment with TAX (100 μg/kg/day) significantly ($p<0.05$) decreased the ACE activity in the aorta, as well as significantly contributed the enzyme's activity which ultimately decreased the production of ROS/RNS by initiating the vascular remodeling. Furthermore, authors also suggested that TAX showed profound beneficial effects in cardiovascular disease (CVD) over quercetin.

Daily uses of flavonoids exert cardio-protective effects and decrease the risk of cardiovascular diseases, especially hypertension. Flavonoids increases nitric oxide (NO) bioavailability, plummeting endothelial cell oxidative stress or curbing vascular ion channel activity. Flavanols, flavanones, flavones, flavonols, anthocyanins, and isoflavones are six different flavonoids reported for their antihypertensive and cardioprotective effects by Maaliki et al. [76].

Duarte et al. [77] explored the antioxidant mediated antihypertensive effect of quercetin. Ahmed et al. [78] compared the anti-hypertensive effects of six isolated flavonoid from three different plants. The flavonoids isoaromadendrin, TAX and 5-hydroxy-3,4′,7-trimethoxyflavon were found to be most potent and decreased the blood pressure to 36.5, 20.0 and 30.0 mmHg respectively at the oral dose of 3.3 mg/kg.

## 3.12. Effects of TAX on osteoclastogenesis

Flavonoids have been confirmed to produce therapeutic effects in osteoporosis as well as in the promotion of bone health [79]. To explore the impacts of TAX on the arrangement and capacity of osteoclast, Cai et al. [80] a Chinese scientist evaluated the TAX for its osteoclastogenesis effects in female C57BL/6 mice. Treatment with TAX repress osteoclast activity and improved ovariectomized-induced bone loss, as well as decreases the serum levels of receptor activator of NF-κB ligand (RANKL), IL-6, IL-1β and TNF-α. *In vitro* study results suggested that TAX also suppresses the activation of NF-κB, C-Fos, and mitogen-activated protein kinase, and decrease osteoclast-specific gene expression. Study results had proven that TAX inhibits osteoclastogenesis via repressing the upstream pathways of RANK signaling. Recently, TAX is recognized as the potential alternative to estrogen replacement therapy to produce promising effects in osteoclastogenesis-related diseases [81].

## 3.13. Diacylglycerol acyltransferase (DGAT) and microsomal triglyceride transfer protein (MTP) inhibitory activity

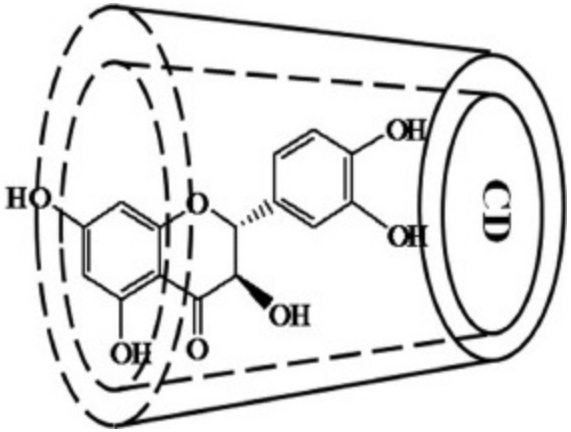
Both DGAT and MTP are involved in triglyceride (TG) biosynthesis [82,83]. Inhibition of DGAT and MTP leads in interruption of TG biosynthesis and lumenal TG content respectively [84,85].

Flavonoid like quercetin has been reported to inhibit TG synthesis, particularly by interrupting DGAT activity. However, the mechanism by which flavonoids interrupt DGAT activity is still unclear [86]. Casaschi et al. [87] examined the role of TAX on apolipoprotein B (apoB) secretion and TG synthesis on HepG2 cells. Study results demonstrated that it reduces the apoB secretion (60% at a concentration of 200 mol/l) as well as inhibited microsomal TG synthesis (41%). TAX also reduced the availability of TG in lumen for lipoprotein assembly by decreasing DGAT activity as well as accumulation of MTP.

## 3.14. Nanoformulations of TAX

Recently herbal nanoformulations gains popularity due to site specific delivery with minimizes side effects [88,89]. Since, TAX possess numerous therapeutic benefits and therefore used in several pharmaceuticals and health care products such and in food industries. However, its poor aqueous solubility restricts its absorption and excessive metabolism, significantly reduced its bioavailability and efficacy. To enhance the bioavailability of TAX, numerous research came into existence, focusing to design and prepare nanoformulation of TAX [90].

Yang et al. [91] prepared and characterized TAX inclusion complexes with cyclodextrin and its derivative: 2-hydroxypropyl-β-cyclodextrin (HPβCD) to improve TAX water-solubility. Formed inclusion complexes showed enhanced water solubility and stability of TAX (Fig.6).




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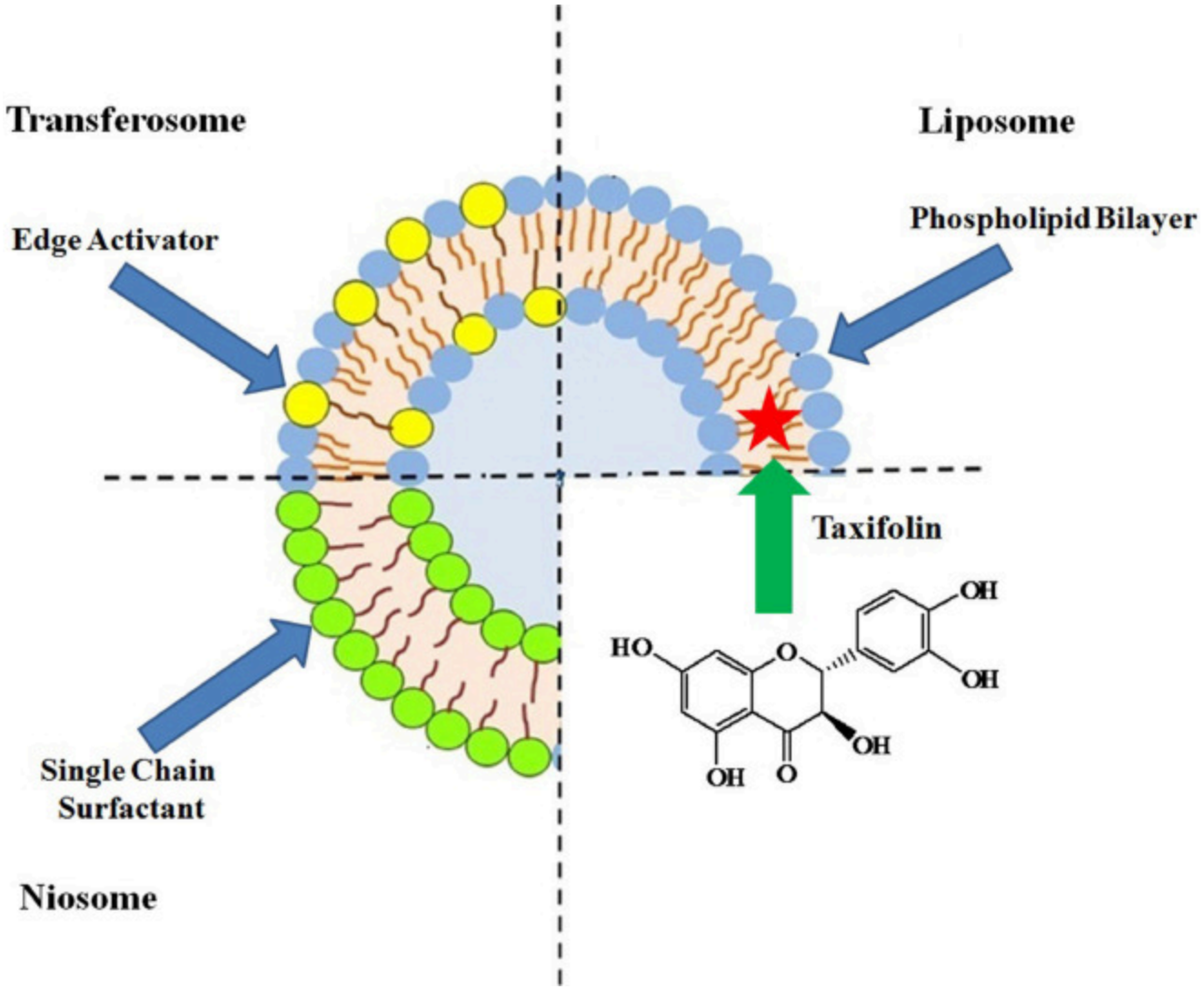
Fig. 6. Inclusion complexes of TXA with varieties of cyclodextrin.

Meanwhile, Chinese scientists Zu and colleagues [92] prepared TAX-β-cyclodextrin nanoparticles to improve TAX bioavailability by liquid anti solvent precipitation (LAP) method. Prepared nanoparticles were characterized by various techniques and for solubility using a dissolution test. The dissolution study revealed the improvement in aqueous solubility of TAX as compared to pure TAX. In addition, TAX nanoparticles showed improved oral bioavailability *in vivo* assay. These results justify the intention of TAX nanoparticles formulation and claimed for great potential value of TAX nanoparticles over free TAX.

Yang et al. [93] developed and validate an ultra-high performance liquid chromatography-MS/MS (UPLC-MS/MS) method to quantify TAX. Authors reported TAX nanodispersion in polyvinylpyrrolidone (PVP) which showed improved oral bioavailability of TAX (0.75%) as compared to plain TAX suspension (0.49%). The formed nanodispersion of TAX was proposed to improve oral bioavailability of TAX compared to plain TAX suspension.

A water-in-oil nano-emulsion of TAX containing Tween 80 as a surfactant had also been developed to increase the bioavailability of TAX [94]. The lipid formulation of TAX in Labrasol had shown 36% increased bioavailability of TAX [95].

Recently, Hasibi et al. [96] prepared TAX-nanovesicles with beneficial properties for health and food preservation. Formed formulations were characterized by suitable techniques and conduct *in vitro* gastrointestinal TAX release studies and stability studies of formulations. Transfersomes showed highest TAX entrapment efficiency with no leakage property and highest antioxidant activity in comparison to liposomes and niosomes (Fig. 7).




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Fig. 7. Schematic representation of nanovesicles including transfersomes, niosomes, and liposomes having entrapped TAX.

## 4. Conclusion

TAX, a flavanonol copied of flavonoids, is a prevalent bioactive component of antioxidant-rich food and dietary supplements, showed distinct range of biological effects including antioxidant, anti-inflammatory, anti-cancer, anti-viral, antibacterial, antidiabetic, anti-acne and play a vivid role in prevention of Alzheimer's disease. Nanoformulation of TAX showed improved bioavailability and sustained release, which increases the use for therapeutic benefits as it is already commercially available in the semi-synthetic form in the market. Consequently, it appears to be considered the use of this dietary flavonoid in human wellbeing, for that further research is unquestionably justified. Further accomplishments will provide new insights and may lead to a new era of TAX based pharmaceutical specialists for the treatment of different illnesses.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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# Phytochemical investigation and in vitro anthelmintic evaluation of extracts of Wild Cinchona (Neolamarckia cadamba Roxb.) fruits

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## Abstract

*Neolamarckia cadamba Roxb.*, a plant commonly used in Indian traditional medicines, has been recognized for its anthelmintic properties. This study aimed to evaluate the in vitro anthelmintic activity of *N. cadamba* fruit extracts against
*Ascaridia galli* (roundworm), *Raillietina spiralis* (tapeworm), and *Pheretima posthuma* (Indian adult earthworm). The hydro-methanolic extract of *N. cadamba* fruits exhibited superior anthelmintic activity compared to the ethyl acetate extract.
Phytochemical analysis of the extracts revealed the presence of phenols, tannins, saponins, glycosides, phytosterols,
flavonoids, and terpenoids. Furthermore, the contents of phenolics, flavonoids, proanthocyanidins, and anthocyanins in the
fruit extracts were quantified. The quantitative analysis of total phenolic content of extracts revealved that hydromethanolic
extract contains higher quantity of phenolics, flavonoids, proanthocyanidins, and anthocyanins in comparision to the
ethylacetate extract. These findings support the observation that hydro-methanolic extract of *N. cadamba* fruits exhibited
superior anthelmintic activity compared to the ethyl



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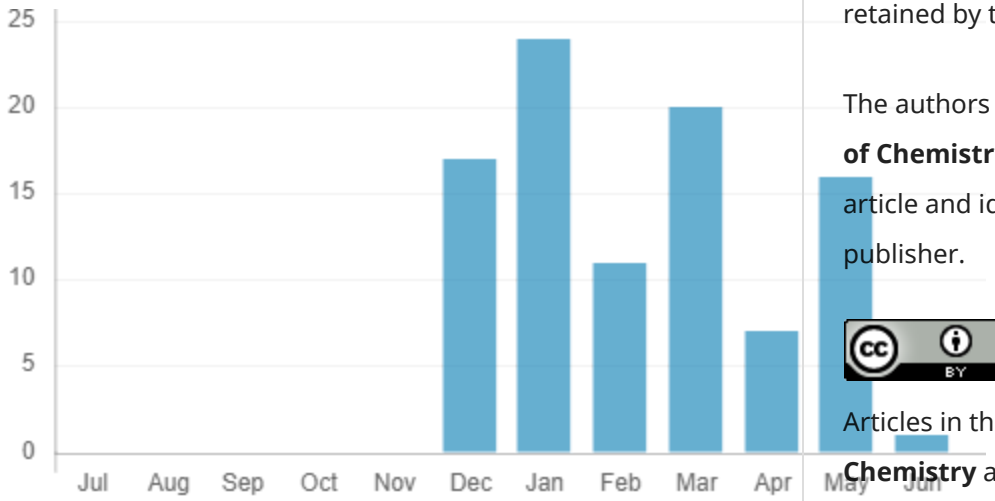


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acetate extract because polyphenolic compounds are well established
for their anthelmintic activity.

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# Design, Synthesis and Anti-tubercular Evaluation of Some Novel Chroman-Hydrazone Derivatives

January 2023 · Asian Journal of Chemistry 35(2):483-492
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DOI:10.14233/ajchem.2023.27002

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Abstract

The molecular docking, synthesis, spectral characterization and anti-tubercular evaluation of 10 novel N'-substituted-6-hydroxy-2,5,7,8-tetramethylchroman-2-carbohydrazide derivatives (SM1-SM10) were reported. The structures of the synthesized derivatives were affirmed by spectroscopic studies such as FTIR, 1H NMR, 13C NMR and high resolution-mass spectrometry. Predicted ADME and toxicity investigations were accomplished to presume the pharmacokinetic parameters of the compounds. The synthesized compounds were evaluated for in vitro anti-tubercular activity against Mycobacterium tuberculosis H37Rv strain using Microplate Alamar Blue Assay (MABA) taking isoniazid, rifampicin, ethambutol, amikacin, streptomycin and levofloxacin as positive drug standards. Compound SM8 has shown the significant anti-tubercular activity among all the titled compounds. The results indicated that chroman-hydrazone skeleton could serve as a lead for the development of novel anti-tubercular drugs.

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Clinical study of dynamic changes of cerebrospinal fluid cytology in drug resistant tuberculous meni...

May 2021 · Chinese Journal of Contemporary Neurology and Neurosurgery

D.-D. Cao · W.-F. Kuang · L.-T. Zhang · [...] · Q.-L. Zhang

Objective: To summarize the dynamic changes of cerebrospinal fluid (CSF) cytology in drug resistant tuberculous meningitis (TBM), and to explore its value in drug resistance and efficacy evaluation of TBM. Methods: Seventy-nine patients with TBM who were diagnosed and treated in Jiangxi Chest Hospital from January 2013 to December 2020 were included in this study. H(S)REZ(V) scheme[isoniazid (or ... [Show full abstract]

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Simon Tiberi

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The efficiency of conventional chemotherapy regimens was comparatively studied in 75 patients with recurrent pulmonary tuberculosis. In the patients with recurrent pulmonary tuberculosis, conventional chemotherapy regimen "2b" including isoniazid, rifampicin, pyrazinamide, ethambutol, fluoroquinolone (ofloxacin, ciprofloxacin, and levofloxacin), and canamycin (amikacin) versus conventional ... [Show full abstract]

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Kaiming Liu

The genotypes of Mycobacterium tuberculosis (M. tuberculosis) have been found to differ in their resistance to different drugs. Although there is a high incidence of tuberculosis (TB) in Jiangxi, knowledge of the genotypes of M. tuberculosis in this province is limited in recent years. In this study, we investigated the relationship between genetic diversity and drug resistance in M. tuberculosis ... [Show full abstract]

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Objectives Adequate anti-tuberculosis (TB) treatment is an important factor that can affect the patient's outcome. Higher mortality is found in patients who do not receive optimal treatment that includes isoniazid and rifampicin. The objective of this study is to evaluate the association of use of alternative TB treatment regimens (without rifampicin and isoniazid) and mortality among patients ... [Show full abstract]

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Today new antibuberculous drugs and new combination regiments have been devevoped against the tuberculous resistance. However, the effects of these drugs on the immune system of the host has not been known yet. The aim of this study was to investigate the in vitro effects of primary antituberculous drugs [isoniazid (INH, 5jug/ml), rifampicine (RIF, 7jug/ml), pyrazinamide (PZA, 40jug/ml). ... [Show full abstract]

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Article

# Antibacterial Potentiality of Isatin-Containing Hybrid Derivatives

March 2023 · Asian Journal of Chemistry 35(4):815-827
March 2023 · 35(4):815-827
DOI:10.14233/ajchem.2023.27632

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Abstract

Antibiotics are critical in the management of a variety of bacterial infections, however, repeated infections produced by relentless bacteria are obstructing effective infection treatment and it is the most significant and vexing problem at the moment. Medicinal chemists face a difficult problem in developing appropriate lead compounds for various diseases, isatin and its hybrids would be one of them due to its versatility in many medications and its derivatives exhibit an extensive variety of structural and mechanistic properties. This review looks at the isatin hybrids that have probable antibacterial action. The structure-activity relationship (SAR) and the way of producing action are also examined in order to locate the course for the intent and expansion of isatin hybrids by means of increased efficacy, reduced toxicity and good pharmacokinetic profiles. Based on the findings, it can be inferred that 3-hydrazone, imine, spiro, oxindole, guanidino and N-alkyl, aryl, acyl substituted isatin hybrids with electronegative groups on other heterocycles have improved bactericidal activity. Furthermore, the antibacterial activity of isatin is dependent on the binding linkage, such as amide (NHCO), carbonyl (CO) or other hetero atom-containing linkers that have improved antibacterial activity. This review gives an idea

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Российский журнал боли
2023, т. 21, № 1, с. 19-25
https://doi.org/10.17116/pain20232101119

# Potent anticonvulsant compounds with anti-hyperalgesic activity i formalin test of hyperalgesia

© PRAVEEN KUMAR[1], LAXMI TRIPATHI[2]

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[2]Department of Pharmaceutical Chemistry, Agra Public Pharmacy College, Delhi-Agra National Highway-2, Artoni, Agra, Utt

**ABSTRACT**

**Objective.** Keeping in view the fact that anti-seizure drugs (ASDs) can frequently reduce pain in various animal models matory and neuropathic pain, the potential of N′-[4-(4-fluorophenoxy)benzylidene]pyridine-4-carbohydrazide PCH 6 an thoxyphenyl)-2-[4-(4-methylphenoxy)benzylidene] hydrazine carbothioamide PT 30 to alleviate the acute and/or inf stages of pain was assessed in mouse formalin test of hyperalgesia.

**Material and methods.** Since, neuropathic pain represents pathological states of abnormal neuronal discharge; the of PCH 6 and PT 30 to alleviate the acute and/or inflammatory stages of pain were estimated in mouse formalin test of h

**Results.** PCH 6 and PT 30 were designed, synthesized and established as a prospective anticonvulsant compounds. PCI 30 exhibited significant anticonvulsant activity in two seizure models namely MES and 6 Hz seizure. At a dose close to PCH 6 exhibited notable reduction in paw licking behavior of mice during the acute and inflammatory stages ensuir injection in the paw. At a dose of 128 mg/kg, PCH 6 showed 61.71% control (SEM 7.525; $p>0.05$) in acute stage a control (SEM 10.81; $p>0.01$) in inflammatory stage of pain in the mouse formalin test of hyperalgesia. At a dose of 100 30 displayed considerable curtailment in paw licking behavior of mice during the acute and inflammatory phases ensu lin injection in the paw. PT 30 showed 61.57% control (SEM 7.71; $p>0.05$) in acute stage and 6.03% control (SEM 2.9 in the inflammatory stage of pain in the mouse formalin test of hyperalgesia.

**Conclusion.** PCH 6 and PT 30 turned up as an effectual anti-hyperalgesic in mouse formalin test and can be explored type in the development of analgesic and anti-inflammatory agent for control of pain in neuropathic pain syndrome.

***Keywords:*** *neuropathic pain syndrome, anticonvulant, anti-hyperalgesic agent, mouse formalin test of hyperalgesia.*

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Yogesh Chand Yadav & Satyanarayan Pattnaik

Pages 240-247 | Received 14 Nov 2022, Accepted 06 Apr 2023, Published online: 19 Apr 2023

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## Abstract

## Objective

The purpose of the study is to assess the bioavailability and neuroprotective effect of hesperetin (Hesp)-loaded nanofibers.

## Methods

Electrospinning was used to create and characterize polyvinyl pyrrolidone-based Hesp-loaded nanofibers. To evaluate the produced nanofibers, preclinical studies were conducted. The study involved five groups of Wistar rats, and the treatments were administered as follows. Group 1 (control) was given regular saline for 14 d. On the 14th day, Group 2 was given scopolamine. Group 3 was given donepezil for 14 d and then scopolamine on the 14th. Group 4 was given Hesp for 14 d and then scopolamine on the 14th. Group 5 was given Hesp-loaded nanofibers for 14 d, followed by scopolamine on the 14th. On the 14th day, rats' memory was tested using Cook's pole climbing apparatus and the Morris water maze (MWM). On the 15th day, rats from each group were slaughtered, brain tissues were separated, and biochemical and histological analyses were performed. In addition, *in vitro* dissolution experiments and pharmacokinetic studies were carried out.

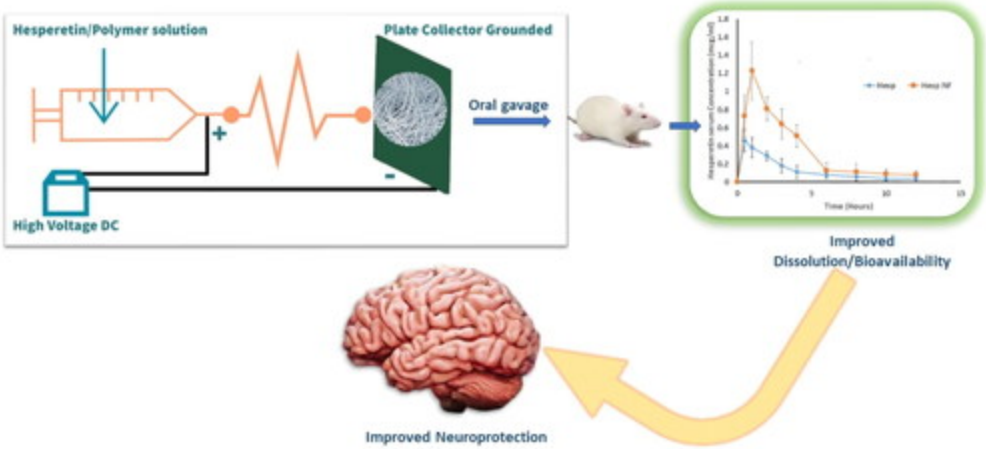
## Results

When compared to the control group, scopolamine-treated rats had considerably longer escape latency times, as well as increased acetylcholinesterase (AChE) activity, lipid peroxidation, degeneration, and inflammation in the hippocampus. These parameters were greatly recovered by donepezil and Hesp-loaded nanofibers that had been pretreated. Because of the greatly improved bioavailability of Hesp, the Hesp-loaded nanofibers significantly protected rats from scopolamine-induced amnesia.

## Conclusions

Hesp-loaded nanofibers have an excellent neuroprotective effect against scopolamine-induced amnesia due to enhanced bioavailability.

## Graphical Abstract




**Keywords:** Hesperetin nanofibers neuroprotection amnesia bioavailability dissolution

## Disclosure statement

No potential conflict of interest was reported by the author(s).

# Additional information

## Funding

The author(s) reported there is no funding associated with the work featured in this article.

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# Effects of hesperetin on dimethylsulphoxide induced cognitive dysfunction mediated through oxidative stress marker and neuroinflammation in hippocampus

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## Abstract

### Objective

Hesperetin is a natural flavonoid with antioxidant potential and can be used to treat disorders of the brain. Therefore, present study is designed to investigate effect of hesperetin on dimethylsulphoxide induced cognitive dysfunction mediated

through oxidative stress marker and neuroinflammation in hippocampus

## Methodology

The experiment was conducted using five treatment groups, each group consisting six rats. Group 1 (control) received 1 ml/kg normal saline interperitoneally for 14 days. Group 2 received 1 ml/kg DMSO per oral for14 days. Group 3 received donepezil 3 mg/kg per day for 14 days and DMSO (1 ml/kg p.o.) for 14th day. Group 4 and 5 received a dose of 25 mg /kg of hesperetin (H1) and 50 mg/kg hesperetin (H2) per oral, per day for 14 days, respectively. Hesperetin was dissolved in DMSO to get 25 mg/ml solution. On 14th day, the memory of rats was assessed by Cook's pole climbing apparatus and Morris water maze test. On 15th day, six rats of each group were sacrificed and the isolated brain tissues were subjected for the estimation of biochemical parameters, beta actin blot analysis and histopathological examination.

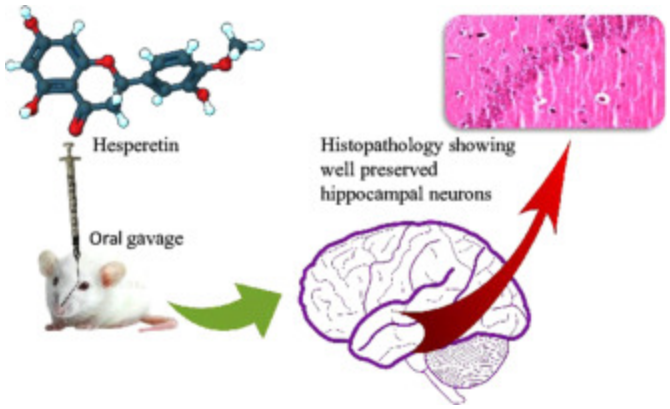
## Results

The DMSO treated rats showed significantly enhanced escape latency time ($P<0.0001$) acetylcholinesterase (AchE) activity ($P<0.0001$), lipid peroxidation ($P<0.0001$), TNF-α level and decreased reduced glutathione levels ($p<0.001$), attenuated beta actin blot density, degradation and inflammation in the hippocampus region as compared to the control group. These parameters were significantly recovered in the rats pretreated with donepezil and hesperetin.

## Conclusion

The findings of this study demonstrated that DMSO induced cognitive dysfunction in rats and hesperetin has potential to improve the cognitive performance against DMSO via reduced oxidative stress and neuroinflammation in hippocampus.

## Graphical abstract




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## Keywords

Dimethyl sulphoxide; Cognitive dysfunction; Hesperetin; Antioxidant; Beta actin signaling

## 1. Introduction

Hesperetin (4′methoxy-3′, 5, 7- trihydroxyflavanone) is a natural flavonoid in Chinese traditional medicine belonging to the flavanone category obtained from citrus plant like lemons and oranges [1,2] and hesperetin contents of the Chinese preparations are CAS 520–33–2 Natural Orange Peel Extract Hesperetin, China Pure Natural *Citrus Aurantium* Extract 98% Hesperitin, etc. It has good antioxidant potential like free radical scavenging and increases cell defense against cell impairments. It can cross blood brain barrier and can treat many disorders of brain [3]. It shows neuroprotective action against hydroxy dioxide induced cytotoxicity owing to its significant antioxidant potential by decreasing of the calcium

concentration and the caspase-3 action [4]. Many studies have reported that hesperetin has good antioxidant, anti-inflammatory properties [5], anti-diabetic [6], antiviral, and neuroprotective action against neurogenerative disorders like Huntington disease, Parkinsonism, Alzheimer, and multiple sclerosis [7], [8], [9], [10], [11]. Despite several pharmacological activity of hesperetin, it has limited therapeutic use because it has poor water solubility and stability [12]. However, hesperetin is soluble in DMSO [13]. Some studies have reported that DMSO induces transient global cognitive dysfunction, neurotoxicity and neuronal damage leading to memory deficits [14,15]. To the best of our knowledge no study reports the effect of hesperetin on experimentally DMSO induced cognitive dysfunction model in rats. Based on this background, the present study has been designed to investigate effect of hesperetin on experimentally DMSO induced cognitive dysfunction in rats.

## 2. Material and methods

Hesperetin (Sigma Aldrich chemicals Pvt. Ltd., India), Acetylcholinesterase activity assay Kit (Sigma Aldrich chemicals Pvt. Ltd. India), scopolamine hydrobromide (Sigma Aldrich chemicals Pvt. Ltd. India), Ellman's reagent [5,5- dithio-bis-2-nitrobenzoic acid (Sigma Aldrich chemicals Pvt. Ltd., India), trichloroacetic acid (Merck chemicals Pvt. Ltd. India), Phosphoric acid (Merck chemicals Pvt. Ltd., India),thiobarbuturic acids (Merck chemicals Pvt. Ltd., India), donepezil hydrochloric acid (Aricept), EDTA (Merck chemicals Pvt. Ltd., India, TBST (Merck chemicals Pvt. Ltd. India), beta actin (SC 47,778, USA), and TNF-α elisa kit (Diaclone, France) were procured.

### 2.1. Experimental animals

All the experimental rats were kept in a 12 h light/dark cycle; at a temperature of 25±1°Ċ and humidity (65±10%). Rats were provided water and food *ad libidum;* however; all the rats were kept on overnight fasting (~12 h) prior to the experiment. The animal experimentation was performed as per guidelines and regulations of the “committee for the purpose of control and supervision of experiments on animals (CPCSEA)”and institution animal ethical committee (IAEC/01/AH/2019–2020) of the Uttar Pradesh University of Medical Sciences, Saifai; Etawah, India has approved this study.

### 2.2. Experimental design

Thirty-six Wistar rats, of either sex, aged 10–12 weeks and weighing 100–150 gm were used in the present study. The rats were divided into five treatment groups, each group consisting of six rats ($n$=6) and the duration of study was 15 days. Group 1 (control) received 1 ml/kg interperitoneally normal saline for 14 days. Group 2 received 1 ml/kg DMSO per oral for 14 days [16]. Group 3 received donepezil 3 mg/kg per day orally for 14 days and DMSO (1 ml/kg per oral) for 14th day. Group 4 and 5 received 25 mg /kg of hesperetin (H1) and 50 mg/kg per day per oral hesperetin (H2) per day per oral for 14 days respectively. Hesperetin was dissolved in DMSO to get 25 mg / ml solution. On 14th day, working memory and long-term memory in rats were tested by experimental paradigms like Cook's pole climbing apparatus, Morris water maze test and on 15th day, six rats of each group were sacrificed and the hippocampus was collected to estimate acetylcholinesterase, lipid peroxidase (LPO) and reduced glutathione (GSH), TNF-α level. Beta actin blot analysis and histopathological examination was also carried out on the isolated fractions.

## 2.3. Behavioral assessment (Non-Invasive procedures)

### 2.3.1. Cook's pole climbing apparatus task

This apparatus was used for memory testing on basis of condition stimuli. The rats ($n$=6) were allowed to move in the chamber for 45 s. Beep sound was turned on as condition stimulus and was allowed to flow electric shock into the floor of grid for 5 s. The rats received training about conditional stimulus i.e., beep sound followed by foot electric shock. After the training, rats were skilled of evading the foot shock by climbing the pole after beep sound and protect itself from electric shock. The time taken by the rats to climb the pole was defined as escape latency time. This time was recorded in seconds to study the cognitive function of rats [17,18].

### 2.3.2. Morris water maze test

The apparatus constituted 150 cm diagonally circular pool in which 60 cm high was occupied with water. Titanium dioxide was added to make the water opaque. A rectangular shaped stage (28×10 cm) was erected and submerged 2 cm below the level of water surface in water that allowed the rats to climb on the top during the test. The temperature of water was maintained at 26±2 °C. The rats ($n$=6) were introduced in water from one side of Morris water maze and the time required

by the rat to grasp on the stage was recorded. The animals received three trials per day for developing learning and memory. The time taken by rats to reach the platform was the escape latency time [19].

## 2.4. Biochemical assay

The rats were sacrificed by ketamine hydrochloride (100 mg/kg i.p.) anesthesia. The brain of rats was dissected out. The hippocampus of brain was isolated and a 10% w/v hippocampus homogenate in ice chilled 0.1 M phosphate buffer, pH 8.0 was prepared using homogenizer [20]. Further, the homogenate was centrifuged using a cooling centrifuge at 1106 g for 10 min. The supernatant was collected for estimation of biochemical parameters as follows.

### 2.4.1. Acetylcholinesterase (AchE) activity

AchE activity was measured in hippocampus of the rat's brain by using commercially available Acetylcholinesterase activity assay kit (Sigma Aldrich chemicals Pvt. Ltd. India). 10% w/v hippocampus was homogenized in 0.1 M phosphate buffer, pH 7.5, further it was centrifuged at 14 000 rpm at 4 °C for 5 min and was collected supernatants for assessments. 10 μl of hippocampus supernatants was added in duplicate to a 96-well plate. Then, 190 μl of the freshly prepared working reagent was added to all sample wells and the plate was tapped to mix. Samples were nurtured at room temperature for 2 min and the initial absorbance was taken at 412 nm followed 10 min later by another absorbance was taken. The calibrator (200 U/l) given in the Kit that was used as a standard. The result of AChE activity has been represented in units/L [21,22].

### 2.4.2. Lipid peroxidation activity

10% w/v homogenate of hippocampus was added in sodium dodecyl sulfate, acetate buffer (pH 3.5), and aqueous solution of thiobarbituric acid. It was heated at 95 °C for 60 min resulting the red pigment produced. It was extracted with n-butanol-pyridine mixture andwas measured absorbance at 532 nm and tetra-methoxy-propane was used as a standard. Lipid peroxidation was determined by estimation of malondialdehyde (MDA) levels expressed as nano moles of MDA/mg of tissue [23].

### 2.4.3. Reduced glutathione levels

It was measured byusing Ellman and Lysko method. 10% (w/v) homogenate of hippocampus was mixed in 5% trichloroacetic acid solution and was centrifuged at 3500rpm for 10min. 50µL supernatant was added with 0.32mol/L disodium hydrogen phosphate and 0.04% 5,5-dithiobis 2-nitrobenzoic acid (DTNB) solution. The yellow-colored substance produced by the reaction of GSH and DTNB. It was measured at 412nm. GSH level was expressed in µ moles/mg of tissue [24].

### 2.4.4. TNF-α estimation

The level of TNF-α was measured by using commercially available ELISA kit following the instructions provided in the kit. Briefly, after the experiments, hippocampus region of the brain was isolated and homogenate was prepared. The hippocampus brain homogenates was used for the estimation of the TNF-α level. The data obtained was presented in pg/mL.

### 2.4.5. Beta actin blot analysis

The hippocampus tissue of the brain was homogenized in radio immunoprecipitation assay buffer. Whole protein concentration was evaluated by Bradford method [25]. The protein contents were isolated by acetone precipitation and Bradford reagent was used for protein quantification. SDS-PAGE test was conducted on the Laemmle with slight modifications principles [26]. The blots were incubated overnight with primary antibody against beta actin in 4°C. The membrane was washed 3 time with tris buffered saline with tween-20 (TBST) then additional incubated at room temperature for 3h with corresponding beta actin HRP conjugated secondary antibody (1:2000 dilutions). Further single washing with TBST, the membranes were developed using an enhanced chemiluminescence substrate (Western Bright ECL HRP substrate, Advansta, Melanopark, California, US) in gel dock system [27]. The quantification of protein was measured by densitometric digital analysis protein bands using Image J software developed by Wayne Rasband (NIH, US).

### 2.4. 6. Histopathology

The rats were sacrificed and the isolated rat brain was fixed in 10% formalin and further stored in 10% 0.1M phosphate buffer, pH 7.0 at 48°C. The brains were implanted in paraffin and stained with hematoxylin and eosin. The hippocampal permanent slides were examined under binocular microscope at 40X magnification [28].

## 2.5. Statistical analysis

All the quantitative analysis was showed in mean±standard error mean. It was executed with one way analysis of variance Tukey's test: compare all pairs of groups by using GraphPad InStat software, *P* value<0.05 was considered.

## 3. Results

### 3.1. Effect of hesperetin on memory and cognition

First we assessed the effect of hesperetin on cognitive function of rats by using Cook's pole climbing Apparatus and the escape latency time was observed. Escape latency time was significantly ($p<0.0001$) increased in DMSO treated group as compared to control group. These were significantly ($p<0.001$), ($p<0.0001$), ($p<0.0001$) decreased in rats pretreated with donepezil, and H1 and H2 groups, respectively (Table 1). Afterwards, the effect of hesperetin on the spatial memory of rats was assessed by Morris Water Maze Task. It was found that DMSO treated rats showed significantly (35.58±2.47 s; $p<0.0001$) increased escape latency time as compared to the control group (11.17±2.28 s); whereas the escape latency time was significantly decreased in pre-treated donepezil (14.35±2.65 s; $p<0.001$), H1 (12.84±2.54 s; $p<0.001$) and H2 (17.50±1.12 s; $p<0.001$) as seen in Table 1).

Table 1. Effect of hesperetin on transfer latency time, escape latency time and GSH, MDA level in the hippocampus of DMSO treated Rats.

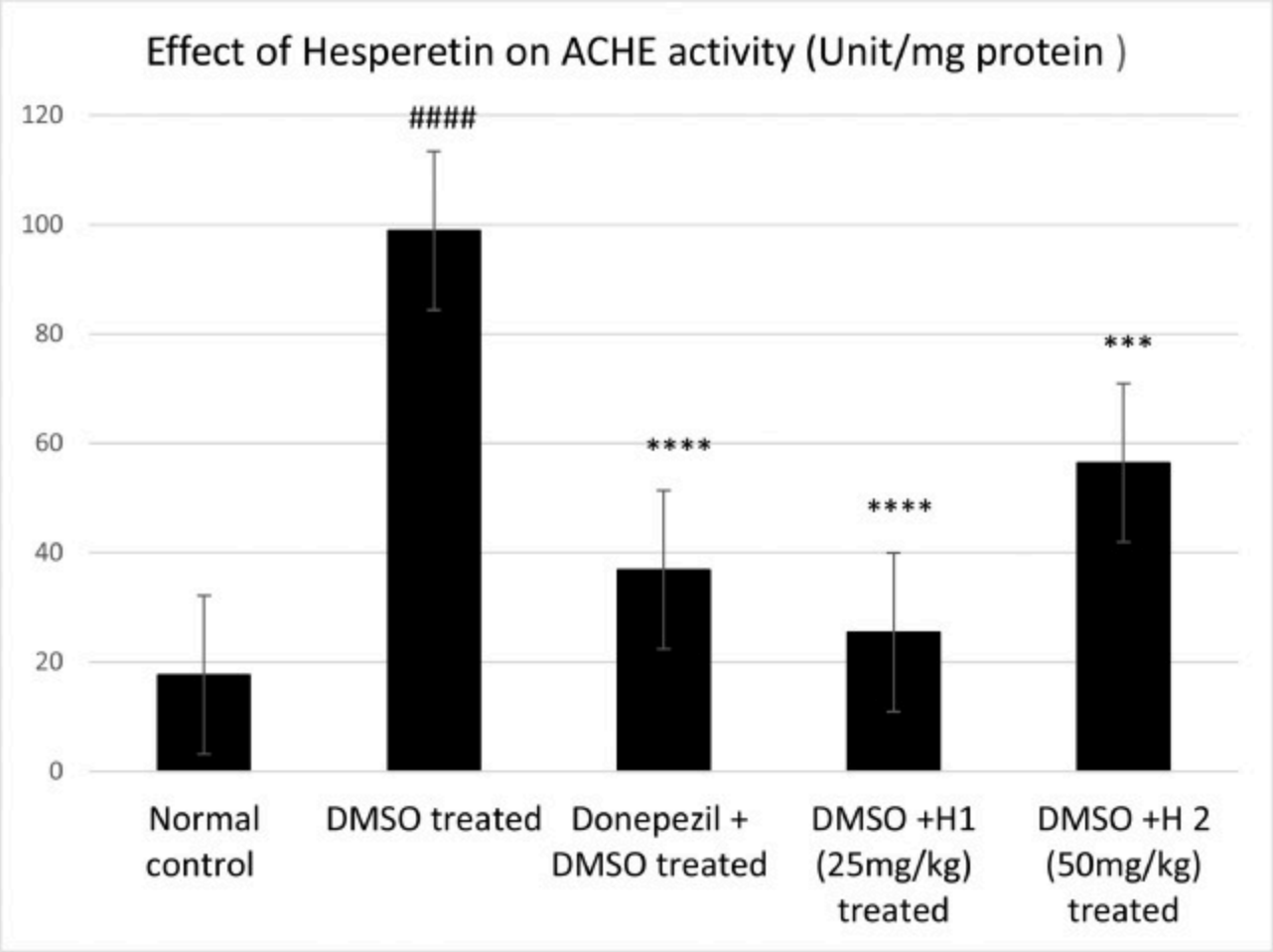
| **Groups** | **Escape latency time Cook's Pole Climbing task (in *sec*)** | **Escape latency time MWT (in *sec*)** | **Reduced GSH μmoles/mg of tissue.** | **Lipid peroxidase nanomoles of MDA/mg of tissue** |
|---|---|---|---|---|
| Control | 3.63±0.66 | 11.17±2.28 | 6.24±0.63 | 5.05±0.39 |
| DMSO treated | 11.33±0.88### | 35.58±2.47#### | 1.54±0.25## | 14.32±0.72#### |
| Donepezil+DMSO treated | 4.66±0.33*** | 14.35±2.65** | 4.28±0.24* | 5.25±0.44**** |
| DMSO +H1(25 mg/kg) treated | 4.48±0.34**** | 12.84±2.54** | 5.25±.75* | 5.16±0.47**** |

| Groups | Escape latency time Cook's Pole Climbing task (in *sec*) | Escape latency time MWT (in *sec*) | Reduced GSH μmoles/mg of tissue. | Lipid peroxidase nanomoles of MDA/mg of tissue |
|---|---|---|---|---|
| DMSO +H2(50mg/kg) treated | 4.50±0.65**** | 17.50±1.12** | 4.37±.83* | 5.66±0.55*** |

Results show mean ± SEM, $n$=6 in each group. Significant differences ###$P$<0.001 and ####$P$<0.0001 compared to the control group with DMSO treated rats and *$P$<0.05, **$P$<0.01, ***$P$<0.001 and ****$P$<0.0001 compared with the DMSO treated to rest of groups.

## 3.2. Effect of hesperetin on acetylcholinesterase (AchE) enzyme level in hippocampus of rat brain

We employ the AchE activity test in the hippocampus of rat brain to measure the neuroprotective impact of hesperitin on Acetylcholinesterase (AchE) enzyme level. Our result showed that the DMSO treatment significantly increased the AchE activity (98.84±11.43; $P$<0.0001) in the hippocampus as compared to the control group (17.60±3.158). On the other hand significantly decreased AchE activity was detected in donepezil (36.84±8.60; $p$< 0.0001), H1 (25.38±3.48; $p$<0.0001) and H2 (56.38±3.48; $p$<0.001) treatment groups, respectively (Fig. 1).




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Fig. 1. Effect of hesperetin on Acetylcholinesterase (AchE) activity in the hippocampus of DMSO treated rats. Result is shown as mean±SEM, $n$=6 in each group. Significance: ####$P$<0.0001 compared to the control group with DMSO treated and ****$P$<0.0001, ****$P$<0.0001, ***$P$<0.001, compared with the DMSO treated group remaining groups.

## 3.3. Effect of hesperetin on GSH and MDA in hippocampus of rat brain

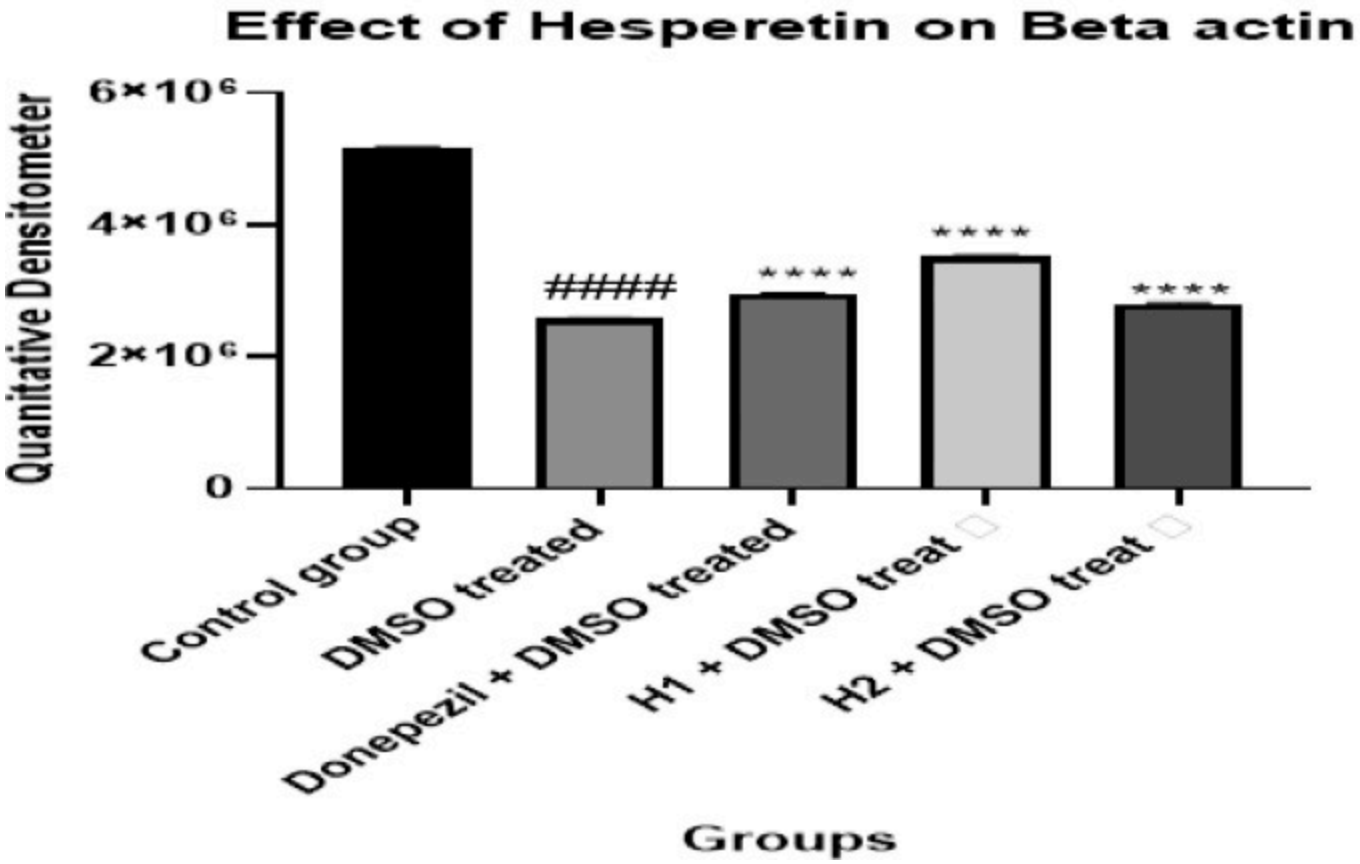
Oxidative stress is major source of neuroinflammation in any neurological disorder. In our study we evaluate the antioxidant effect of hesperetin by assessment antioxidant enzymes such as glutathione. Present data conclude that DMSO treated group exhibited significantly reduced GSH level ($p< 0.01$; 1.54±0.25) as compared to the control group (6.24±0.63) whereas donepezil, H1 and H2 treated rats showed significantly increased reduced GSH ($p<0.05$; 4.28±0.24), ($p<0.001$; 5.25±.75), ($p<0.05$; 4.37±.83) (Table 1).

Moreover lipid peroxidation in terms of MDA level was quantified. Results depicts that DMSO treated rats showed significantly ($p<0.0001$; 14.32±0.72) increased lipid peroxidase as compared to the control group (5.05±0.39) which significantly decreased in the group pretreated with donepezil ($p<0.0001$; 5.25±0.44), H1 ($p<0.0001$; 5.17±0.47) and H2 ($p<0.001$; 5.66±0.55) (Table 1).

## 3.4. Effect of hesperetin on immunoblotting of hippocampus of rat brain

The DMSO treated rats showed significantly decreased ($p<0.0001$) beta actin blot density as compared to the control group indicating that DMSO suppressed beta actin expression levels in the hippocampus. However, the groups pretreated with donepezil, and H1 (25 mg/kg) and H2 (50 mg/kg) recovered beta actin expression levels significantly ($p<0.0001$), ($p<0.0001$), ($p<0.0001$) respectively. Hesperetin promoted expressions of beta actin protein in the hippocampus of DMSO treated rats (Fig. 2).




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Fig. 2. Effect of hesperetin on the protein expressions of Beta actin in the hippocampus of DMSO treated rats. Data is represented as the mean±SEM, $n$=6 in each group. Significant differences ####$P$<0.0001 compared to the control group; ****$P$<0.001, ****$P$<0.001, and ****$P$<0.001 compared with the DMSO group.

## 3.5. Effect of hesperetin on histopathology of hippocampus of rat brain

The hippocampus of control group rats showed normal cornusammonis area (CA3, CA2, CA1 CA2), glial cells among the neuronal process, and the dentate gyrus was normal [Fig.3, Plate 1 (a)].

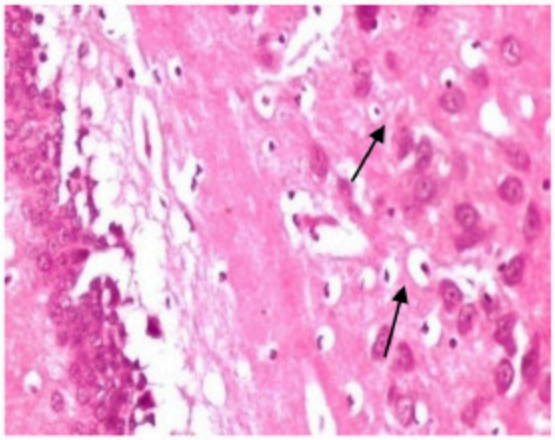


**Plate 1 (a) Control group**

Molecular and granular layers degeneration and reduce neurons

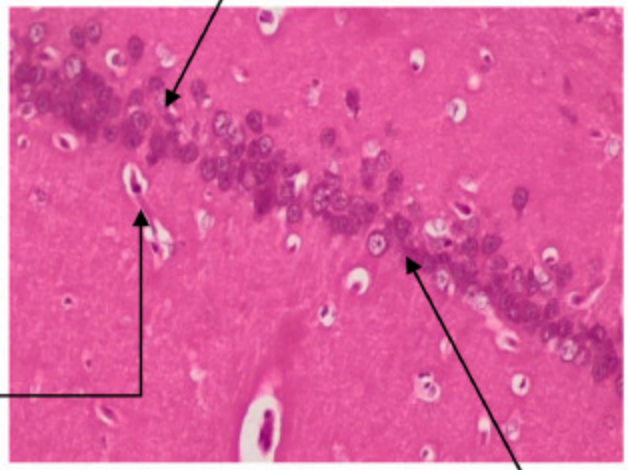


**Plate 1(b) DMSO treated groups:**

Eosinophil Moderately inflammatory

Neuronophagia

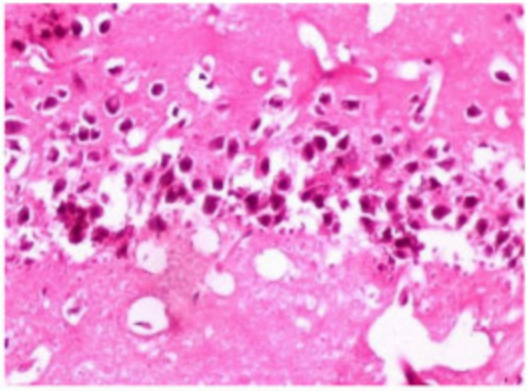


**Plate 1 (c) Donepezil + DMSO treated**

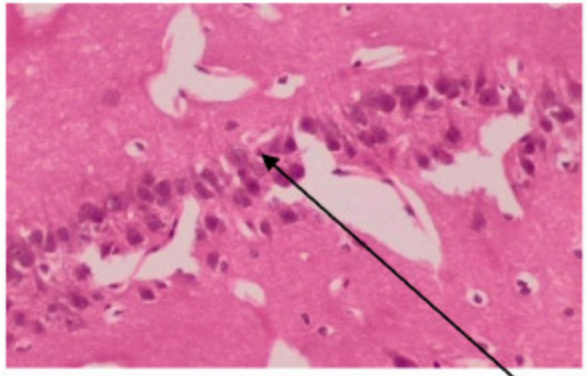


**Plate 1 (d) H1+ DMSO treated**

Neurons well preserved



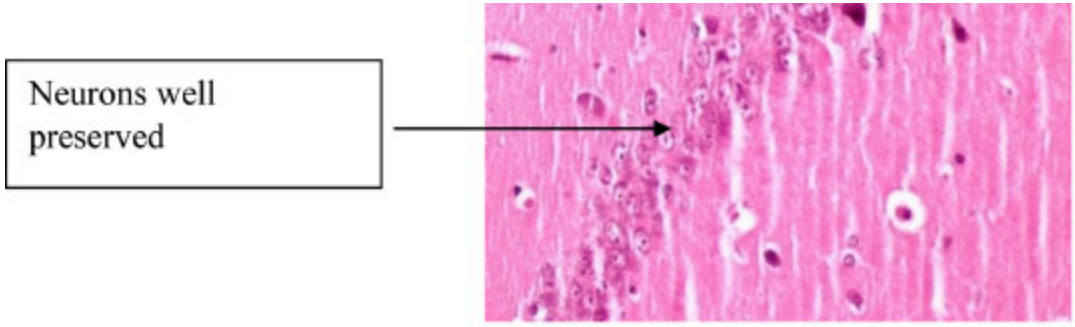



**Plate 1 (e) H2 + DMSO Treated**

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Fig. 3. DMSO treated rat's hippocampus showed scattered nerve cells, pyramidal cells degeneration, neuronophagia and thickened endothelium of blood vessels with moderately inflammatory cells like eosinophil in Plate 1(B1 & B2) as compared with control group Plate 1 (A1 &A2) which was significantly recovered in pretreated Donepezil Plate 1 (C1 & C2), H1 Plate 1(D1 & D2) and H2 Plate 1 (E1 & E2) on 40 X. (e) H2+DMSO Treated.

The DMSO treated rats showed significantly degenerative changes n the dentate gyrus and chromatolysis. Molecular and granular layer were markedly thinned out and degenerative changes were reported. Pyramidal cell showed neurophgia and per cellular edema. The neurons were degenerated and reduced, and few inflammatory cells were observed [Fig.3, Plate 1(b)].

**Donepezil+DMSO treated group:** The cortex layer was normal and well organized and the dentate gyrus was less degenerated as compared to the DMSO treated group [Fig.3, Plate 1(c)].

**H1+DMSO treated rats:** The hippocampus showed well preserved dentate gyrus, compact granular cells, preserved neuronal process of molecular layer and the purkinje cells were well organized [Fig.3 Plate 1(d)].

**H2+DMSO treated:** The hippocampus region showed proper hippocampus and dentate whereas dentate gyrus was loosely arranged but showed neuronal process. Purkunje cells were well preserved [Fig.3, Plate 1(e)].

Thus the groups pretreated with H1 and H2 showed normal hippocampus and well organized glial cells among the neuronal processes but minimal inflammatory cells were also present, predominantly eosinophils (Fig.3).

## 3.6. Effect of herperetin on proinflammatory cytokine TNF-α level

Since proinflammatory cytokines like TNF-α are a key regulator of neuroinflammation, we used an ELISA kit to check the TNF-α level in the rat brain to assess the neuroprotective potential of hesperetin. We analysed that DMSO treated group exhibited increased hippocampal TNF-α level (18.21±0.93pg/mL) as compared to the control group (4.25±0.56pg/mL; $p<0.001$) whereas donepezil, H1 and H2 treated rats successfully rescued the neurotoxic effect of DMSO and showed significant reduction in TNF-α level in rat hippocampus area of brain [9.51±0.73pg/mL, 5.96±0.93pg/mL, and 6.41±1.23pg/mL; $p<0.001$), respectively (Table2).

Table 2. Effect of Hesperetin on DMSO induced changes in TNF-α level in hippocampus region of the brain.

| Groups | TNF-α level (pg/mL) |
|---|---|
| 1. Control | 4.25±0.56 |
| 2. DMSO Group (1ml/kg) | 18.21±0.93$^{###}$ |
| 3. Donepezil (3mg/kg)+DMSO Group (1ml/kg) | 9.51±0.73$^{***}$ |
| 4. Hesperetin (H1) (25mg/kg)+ DMSO Group (1ml/kg) | 5.96±0.93$^{***}$ |

| Groups | TNF-α level (pg/mL) |
|---|---|
| 5. Hesperetin (H2) (50 mg/kg)+ DMSO Group (1 ml/kg) | 6.41 ± 1.23*** |

Results show mean ± SEM, $n$=6 in each group. Significant differences ###$P$<0.001 and compared to the control group with DMSO treated rats and ***$P$<0.001 compared with the DMSO treated to rest of groups.

## 4. . Discussion

The present study revealed that hesperetin has neuroprotective effect against DMSO induced cognitive dysfunction in rats. The results data of Cook's pole climbing test, and MWM screening indicated that hesperetin administration lightened the cognitive dysfunction by preventing the DMSO toxicity. Actually, the treatment with Hesperetin and DMSO was simultaneous, and therefore the protective effects may be a mere consequence of preventing the onset of DMSO toxicity.

The Cook's pole climbing tests evaluated longstanding memory created on adverse strengthening in rats [29]. This test data showed the escape latency time was significantly increased in DMSO treated group as compared to control group and it was significantly decreased in the groups pretreated with donepezil and hesperetin (H1 & H2) that clearly indicated that H1 and H2 can significantly improve memory in the DMSO treated rats.

MWM test assessed the long term, spatial learning aptitude [30]. In the MWM test, scopolamine treated rats showed significantly increased escape latency time as compared to the control groups rats that indicated DMSO impaired spatial learning and long-term memory and these escape latencies were significantly recovered by pretreated donepezil, H1 and H2. Cognitive functions are regulated by the central cholinergic neurotransmission and the drugs could affect the concentration of cholinergic transmitters that leads to alteration in the performance of memory and learning [31,32]. Thus, optimal concentration of neurotransmitter is needed to maintain normal cognitive function. Rajput and Sarkar reported that chronic genistein treatment significantly improved the cognitive performance in diabetic mice by decreasing AchE activity [33]. Lu et al. also reported that administration of genistein inhibits AchE activity resulting in increased acetylcholine and cholinergic neurotransmission leading to improved cogitative function [34]. These research outcomes support the results of our present study.

Many previous studies have well documented that the oxidative stress mediated pathogenesis of neurodegenerative disorders can be protected by the natural antioxidants like flavonoids specifically the impairment of hippocampus brain cells that leads to cognitive dysfunction [35,36]. Hesperetin scavenges oxygen-derived free radicals and activates antioxidant activity [37,38]. Therefore, in our present study DMSO treated group showed significantly decreased GSH level and increased MDA levels in the hippocampus of rats that indicated oxidative stress in hippocampus DMSO treated rats.

Hesperetin treatment significantly increased the GSH content and decreased the MDA level in the DMSO treated rats. It indicates good antioxidant potential of hesperetin. Therefore, based on these results, it can be concluded that hesperetin can afford protection against DMSO induced cognitive dysfunction through enrichment of the antioxidant action and cholinergic neurotransmission in rats.

Additionally, histopathological studies demonstrated that the DMSO treated rats showed degenerative changes chromatolysis, neuronophagia and thickened endothelium of blood vessels with perivascular and pericellular edema and moderately inflammatory cells like eosinophils. These were significantly restored as normal hippocampus and well organized glial cells among the neuronal processes in the groups pretreated with donepezil, and hesperetin (25 mg/kg and 50 mg/kg) that proved the protective effect of hesperetin against DMSO induced hippocampus impairments.

Hesperetin treated rats have also significant reduction in TNF-α level in rat hippocampus area of brain which is also proven that protective effect of hesperetin against DMSO induced hippocampus impairments.

Further, the beta actin blot analysis demonstrated that the DMSO treated rats showed significantly decreased beta actin total volume density compared to the control group that indicated DMSO suppressed beta actin expression levels in the hippocampus. Previous study has reported that Beta-actin can activate endothelial nitric oxide synthesis (eNOS) thereby enhancing NO production [39]. It is thus proposed that in DMSO treated rats a significant decrease in beta actin resulted in decreased NO production due to cerebrovascular endothelial dysfunction and reduced cerebral blood flow leads to progressive learning and memory disorders; and cognitive dysfunction further develops dementia [40], [41], [42]. However, in the rats pretreated with hesperetin demonstrated a significantly increased concentration of beta actin and acetylcholine resulting in increased production of NO and increased cerebral blood flow that afforded neuroprotection against DMSO induced cognitive dysfunction in rats. Thus, it is a possible mechanism of action of hesperetin as neuroprotective against DMSO induced cognitive dysfunction in rats.

**This study has some limitations**: A careful literature study revealed no reports establishing the effect of hesperetin an experimentally dimethylsulphoxide induced cognitive dysfunction in rats. Moreover, TNF-estimation**,** histopathological examination and western blot analysis are also not reported so far to assess the cognitive function of hesperetin in an experimental rat model. Our study has paved the way for further scientific validation of the efficacy of traditional Chinese medicine product like hesperetin to improve cognitive functions. Further, clinical investigations are to be initiated to evaluate the effectiveness of the studied hesperetin.

## 5. Conclusion

DMSO treated rats inhibit cholinergic neurotransmission, lengthening antioxidant system and deactivating the beta actin signaling resulting in decreased NO production due to cerebrovascular endothelial dysfunction and reduced cerebral blood flow leads to memory depletion that indicated DMSO induces cognitive dysfunction in rats. Hesperetin pretreated rats showed enhanced cholinergic neurotransmission, potentiating the antioxidant system and activating the beta actin signaling resulting in enhanced cerebral blood flow that leads to progressive learning and memory of rats. Therefore, on the basis of present investigation, we may conclude that hesperetin has excellent neuroprotective effect against DMSO induced cognitive dysfunction in rats and improved cognitive performance.

## Ethics approval and consent to participate

It confirmed that animal experiment was performed in accordance with the regulations and guidelines of “committee for the purpose of control and supervision of experiments on animals (CPCSEA)” and institution animal ethical committee (IAEC/01/AH/2019–2020) of the UP University of Medical Sciences, Saifai, Etawah, UP, India has approved.

## Human and animal rights

No humans were used for studies that are the basis of this research. The reported experiments on animals are in accordance with the US National Research Council's "Guide for the Care and Use of Laboratory Animals.

## Consent for publication

Not applicable.

## Availability of data and materials

The data supporting the findings of the article is available within the article.

None.

## Declaration of Competing Interest

The author declares no conflict of interest, financial or otherwise.

## Acknowledgments

Declared none.

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Short Communication

# Investigation of the Asyogh's rectangular device for learning and memory testing in Wistar rats

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- Open
- Associated Video

Metrics

## Abstract

This study aimed to design Asyogh's rectangular device that is used for memory testing in rodents. It was found that scopolamine (3 mg/kg i.p.) and diazepam (1 mg/kg i.p.) caused significant memory deficits in rats, as evidenced by increased transfer latency times. However, these memory deficits were significantly reversed when the rats were pretreated with Donepezil. It further demonstrates that pretreated donepezil is able to effectively restore the memory deficits induced by scopolamine and diazepam, as indicated by the significant recovery in TLT. The present study showed that the device used to measure transfer latency time that was a valuable tool for assessing memory and cognitive function in rodents.

# Introduction

TThe memory is cognitive function that involves the encoding, storage, and retrieval of information in the brain.[1] Memory deficit is called amnesia. The amnesia may be developed due to brain damage, disease, or used of sedatives and hypnotic drugs.[2] The previous studies have been well established the contribution of the cholinergic system in cognitive function of living being.[3] The declined cholinergic function could be induced memory impairment due to either structural lesion or antagonist muscarinic and nicotinic receptor.[4] Scopolamine (anticholinergic drug) induces amnesia due to cholinergic system modulation in animals.[5,6] The previous study reported that diazepam induces amnesia in rats.[7] Present scenario, many apparatus are used in memory testing in rodents. Morris Water Maze apparatus is used to evaluate cognitive functions of rodents.[8] The passive avoidance test is a commonly used to examine long-lasting cognitive functions related to harmful experience in rodents.[9,10] Disadvantage of Morris water maze test, rodents were wetting in water and fill fear and in passive shock avoidance test, memory and learning achieved in rodents through electric shocks. The electric shock induced threatening and fear in rodents and also needed lot of training besides being torturous and painful. These problems can overcome by the present invented Asyogh's rectangular device, which provide memory on the basis of olfactory sensation of food material with rodent friendly and without inducing threaten like electric shock and fear of water.

# Materials and Methods

## Design of Asyogh's rectangular device

It is rectangular shape and size 42" × 20" × 6" and roof covered with wire gauge. In middle of apparatus has 2.5" wide horizontal tunnel and it joined by 6 square boxes from both side right and left. This apparatus has been four points that is accounted from near to the door point, one, two, three and four point. The door point (initial point) instrument opened for keeping animals and four points (target point) closed with rectangular shaped box containing food material and drinking water in bowl at another end shown in Figure 1a and the asyogh's rectangular device 1b and 1c.


F1
Figure 1:
(a) Design of Asyogh's rectangular device, fabricated apparatus (b) Asyogh rectangular device, (c) Asyogh's rectangular device

## Animals

All rats were permitted to have an access to water and food *ad libitum*, and the room temperature was maintained at around 25°C and humidity around 65%. In addition, the rats underwent a fasting period of 12 h before the experiment. The experiment was conducted under the rules of the committee for the purpose of control and supervision of experiments on animals and IAEC, UPUMS, Saifai, Uttar Pradesh.

Training rats: 60–100 g, 10–12 weeks young either sex rats were used. Rats were kept overnight fasting and further rats were kept initial point of the device and rats were allowed to reach at target point of the device where food material located. Rats were very frequently learn and memorized about food location material. Trained rats were divided into five groups and each group consisted of six rats.

Control group (Group I) received 1 ml/kg i.p. normal salt solution (0.9% NaCl) for 14 days. Scopolamine treated (Group II) received intraperitoneal injection scopolamine (3 mg/kg) just 30 min before the testing on the $14^{th}$ day. Diazepam treated (Group III) received intraperitoneal injection diazepam (1 mg/kg) just 30 min before the testing on the $14^{th}$ day. Group IV: pretreated with donepezil (3 mg/kg/day/oral) for 14 days and scopolamine (3 mg/kg intraperitoneal) just 30 min before the testing on the $14^{th}$ day. Group V: pretreated with donepezil (3 mg/kg/day/oral) for 14 days and diazepam 1 mg/kg intraperitoneal just 30 min before the testing on the $14^{th}$ day. On the day $14^{th}$, learning memory in rats was evaluated on basis transfer latency time (TLT) using a novel Asyogh's rectangular device.

The time required to transfer of rats from initial point to target point called TLT. The increase or decrease in the TLT indicated decreasing or increasing memory and learning ability of rats, respectively.

### Statistical analysis

One-way ANOVA were used to compare multiple groups, followed by Dunnett's test for specific group comparisons. The results data considered statistically significant with a P-value less than 0.05.

## Results

TLT of scopolamine treated rats were significantly ($P < 0.0001$) increased 30 sec [shown in Video 1] with compared with TLT of control group 5 sec [shown in Video 2] that was significantly ($P < 0.0001$) recovered 8 sec [shown in Video 4] by pretreated Donepezil group [Figure 2].

F2

Figure 2:

Transfer latency time of scopolamine and pretreated donepezil using novel Asyogh's rectangular device test. Results showed means ± standard error of mean, $n = 6$ in each group. Significant differences IJP-55-395-g00322.jpg $P < 0.0001$ compared to the control group and ****$P < 0.0001$ compared with the scopolamine-treated group

TLT of diazepam treated rats were significantly ($P < 0.001$) increased 20 sec [shown in Video 3] with compared with TLT of control group 5 sec [shown in Video 2] that was significantly ($P < 0.001$) recovered 9 sec [shown in Video 5] by pretreated Donepezil group

[Figure 3].


Figure 3:
Transfer latency time of diazepam and pretreated donepezil by using novel Asyogh's rectangular device test. Results showed means ± standard error of mean, $n = 6$ in each group. Significant differences $^{###}P < 0.001$ compared to the control group and $^{***}P < 0.001$ compared with the diazepam-treated group

# Discussion

Group 2 (scopolamine treated rats) led to significant increased TLT as compared with Group 1.Which was indicated that scopolamine induced cognitive impairment due to its ant cholinergic property that was significantly recovered by pretreated Donepezil. It indicated that the effect of scopolamine was abolished by donepezil and rats become normal.

Previous studies reported that scopolamine experimentally induced amnesia or cognitive impairment.[11,12]

Diazepam-treated rats showed that TLT was significantly increased as compared with Group 1 which be significantly recovered by pretreated donepezil. It indicated that diazepam induced amnesia in rats due to their sedative effect. Actually, diazepam activated gamma amino butyric acid receptor caused by impair memory in rat Zarrindast *et al.* 2002.[13]

Previous studies reported that daizepam and amnesia or cognitive impairment and antianxiety effect in rodents.[14,15]

Actually, pretreated donepezil is improving memory in rats probably due to its capacity to inhibit acetyl cholinesterase activity in brain that leads to prevents the breakdown of acetylcholine resulting enhances concentration of acetylcholine at the synapses which helps to enhancing cholinergic performance which was helpful to improve cognitive functions in rats. The present study data indicated that Asyogh's rectangular device has been justified their objective as memory test in rats. Therefore, this device may best device to be well evaluated cognitive functions rat on basis of TLT with natural ventilation and rodent friendly.

# Conclusion

It is concluded that the Asyogh's rectangular device is well-suited for testing learning and memory in rats. Furthermore, it suggests that this device can be effectively used to evaluate the memory-enhancing effects of drugs. Additionally, it may have potential applications in screening for antianxiety drugs in future research.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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**Keywords:**

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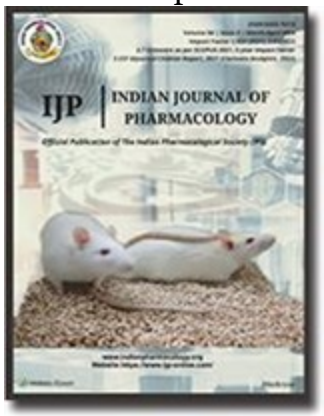
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*Section A-Research paper*
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# Pharmacological evaluation of *Phyllanthus Niruri* leaves for antiulcer activity

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**Abstract**

In the current study, we explored the potential of hydroalcoholic and petroleum ether extracts derived from *Phyllanthus niruri* (L) leaves in addressing antisecretory and antiulcer effects. These extracts were administered orally at varying doses (100, 200, and 400 mg/kg) and evaluated using ethanol-induced ulceration, and cold stress-induced ulceration. Notably, both extracts exhibited significant protection against ulcers, particularly at the highest dose of 400 mg/kg, when compared to the standard treatment.To substantiate the antiulcer potential of *Phyllanthus niruri,* we examined its capacity to scavenge free radicals through lipid peroxidation assays. The results revealed a noteworthy level of antioxidant activity in the extracts. This antioxidant property may be attributed to the presence of flavonoids and polyphenols within the extracts. In summary, our findings suggest that both hydroalcoholic and petroleum ether extracts obtained from the leaves of *Phyllanthus niruri* possess gastric ulcer-protective properties, making them promising candidates for further investigation and potential therapeutic application.

***Keywords:*** *Phyllanthus Niruri*, Antiulcer, Ethanol, pylorus ligation, stress, flavonoids

## 1.0 Introduction

Peptic ulcers, characterized by erosions or open sores in the mucous lining of the stomach, duodenum, or esophagus, represent a prevalent gastrointestinal disorder

affecting millions of individuals worldwide. The pathogenesis of peptic ulcers is multifactorial, with factors such as Helicobacter pylori infection, excessive gastric acid secretion, and impaired mucosal defense mechanisms playing pivotal roles in their development. Despite advancements in medical science and the availability of various therapeutic interventions, the management of peptic ulcers remains a clinical challenge due to the frequent recurrence of symptoms and the potential for complications such as bleeding, perforation, and gastric malignancy (1).

Traditionally, medicinal plants have been used across diverse cultures as a source of remedies for various ailments, including gastrointestinal disorders. One such plant with a rich history of traditional use for its potential antiulcer properties is *Phyllanthus niruri*, commonly known as "Chanca Piedra" or "Stone Breaker." This small, herbaceous plant is native to tropical regions and has been employed for centuries in traditional herbal medicine systems, particularly in Ayurveda, as a remedy for digestive issues, including ulcers (2).

*Phyllanthus niruri* is known for its multifaceted pharmacological profile, with reported activities including antioxidant, anti-inflammatory, hepatoprotective, and antimicrobial effects. Of particular interest is its reputed potential to mitigate the development and progression of peptic ulcers. Recent scientific investigations into the bioactive constituents of *Phyllanthus niruri* have provided insights into the mechanisms underlying its antiulcer activity, leading to a growing interest in exploring its therapeutic potential (3).

This pharmacological evaluation aims to delve into the antiulcer properties of *Phyllanthus niruri* leaves, shedding light on the plant's mechanisms of action and assessing its efficacy in experimental models of peptic ulcers. By understanding the biochemical and physiological processes through which *Phyllanthus niruri* exerts its effects, we hope to pave the way for the development of novel, natural-based therapeutic strategies that can complement or enhance existing treatments for peptic ulcers. This research holds the promise of not only providing insights into the mechanisms of action of *Phyllanthus niruri* but also potentially offering a safer and more sustainable alternative for the management of peptic ulcers, which remains a significant health concern globally (4,5).

## 2.0 Materials and methods

### *2.1. Plant material*

Locally sourced *Phyllanthus niruri* leaves were gathered for this study. These leaves underwent authentication by a respected botanist, and a voucher specimen has been carefully preserved for future reference. The sun-dried flower powder was then subjected to an exhaustive and continuous hot extraction process in a Soxhlet apparatus, utilizing both petroleum ether and a hydroalcoholic solution (composed of 70% water and 30% alcohol). Qualitative analysis was employed to identify the chemical constituents within both extracts. Subsequently, the obtained masses were thoroughly dried and stored in a sealed container under cold conditions to ensure their preservation for subsequent utilization (6).

### *2.2. Experimental animals*

For the study, we chose albino rats and mice, regardless of their gender, with body weights falling within the range of 150 to 230 grams. Ethical approval for the experimental protocol was obtained from the Institutional Animal Ethics Committee, ensuring compliance with established ethical standards for animal research. The animals were housed and cared for in accordance with standard conditions, maintaining a controlled environment. They were provided with unrestricted access to a standard dry pellet diet and water, following strict hygiene practices to ensure their well-being.

### 2.3. *Toxicity study*

We conducted an acute toxicity study following OECD guidelines to determine the $LD_{50}$ (lethal dose for 50% of the population) for both extracts of *Phyllanthus niruri* leaves *(PNL)*. Female albino mice weighing between 20 to 30 grams were employed for this investigation. The animals were meticulously monitored for a period of 12 hours to detect any alterations in their behavioral responses. Mortality was observed over the course of 24 hours following administration of doses at 100, 200, and 400 mg/kg via oral administration. These dose levels were selected based on preliminary results (7).

### **2.4. Ethanol-induced acute gastric ulcers** (8)

Thirty-six rats underwent an 18-hour fasting period, during which they were permitted unrestricted access to water. Subsequently, they were randomly assigned to one of six treatment groups, which included a normal control group, a toxicant group, and three groups receiving varying doses (low, medium, and high) of petroleum ether and hydroalcoholic extracts. All rats were administered 0.5 ml of 70% ethanol orally, with the toxicant group receiving only ethanol. One hour following this administration, all animals were euthanized using ether anesthesia. Their stomachs were then removed and examined for the presence of ulcers, which were scored on a subjective 0-3 point scale. The ulceration index for each stomach was calculated as the sum of these scores.

### **2.5. Cold stress-induced acute gastric ulcers** (9, 10)

In this experimental procedure, both male and female Wistar rats with body weights ranging from 150 to 200 grams underwent a 24-hour fasting period while being allowed access to water. All groups received herbal drug therapy for duration of 7 days. On the 7th day, after an overnight fast, the rats were placed in a metallic restraint chamber 30 minutes following the administration of the test drug. They were then immobilized in a refrigerator maintained at temperatures between 4 to 6 degrees Celsius for duration of 2 hours. After the immobilization period, the rats were humanely euthanized via cervical dislocation, and their stomachs were surgically removed for ulcer assessment. Ulcers were quantified using a subjective 0-3 point scale, and the ulceration index for each stomach was computed by summing the scores.

### **2.6 Method for estimation of lipid peroxidation** (11)

To assess lipid peroxidation levels, we employed the thiobarbituric acid reactive species (TBARS) assay, utilizing malondialdehyde (MDA) as a standard, following the Buege and Aust method. Specifically, we mixed 1.0 ml of the sample extract with 2.0 ml of the TCA-TBA-HCl reagent, which comprised 15% w/v trichloroacetic acid (TCA), 0.375% w/v

thiobarbituric acid (TBA), and 0.25 N hydrochloric acid (HCl). The mixture was then subjected to boiling for 15 minutes, followed by cooling and subsequent centrifugation at 10,000 rpm to eliminate any precipitates. Finally, the absorbance was measured at 535 nm, and the concentration of malondialdehyde in the sample was determined using an extinction coefficient of 1.56 x 105 M -1 cm -1.

## 3. Results

### *3.1 Effect of PE and HAL extracts of PNL on ethanol-induced gastric ulcers:*

Pretreatment of rats with either PE or HAL extract of *PNL* produced a dose dependent protection from ethanol induced ulceration, as compared to control animals. However, the protection was statistically significant at higher dose 400mg/kg. Lansoprazole (8mg/kg) produced significant gastric ulcer protection as compared to control group. (Table 1).

### 3.2 Effect of PE and HAL extracts of *PNL* on cold stress-induced gastric ulcers:

Pretreatment of rats with either PE or HAL extract produced a dose dependent protection from the cold stress-induced ulceration, as compared to control animals. The protection was statistically significant at high dose. Lansoprazole (8mg/kg) produced significant protection as compared to control group (Table 2).

## 4. Discussion

The pharmacological evaluation of *Phyllanthus niruri* leaves for antiulcer activity has provided valuable insights into the potential therapeutic benefits of this natural remedy in managing peptic ulcers. Peptic ulcers are a common gastrointestinal disorder with multifactorial etiology, and their effective treatment remains a clinical challenge. In this discussion, we will examine the findings of the study, consider the mechanisms underlying *Phyllanthus niruri's* antiulcer activity, and discuss the implications of these results. The study demonstrated that both hydroalcoholic and petroleum ether extracts of *Phyllanthus niruri* leaves exhibited significant protection against ulcers. This finding is consistent with traditional medicinal uses of the plant and suggests its potential as an effective antiulcer agent. The dose-response relationship observed in this study is noteworthy. The highest dose (400 mg/kg) appeared to provide the most substantial antiulcer effect. This suggests that the effectiveness of *Phyllanthus niruri* may be dose-dependent, which is an important consideration for potential therapeutic applications.

To support its antiulcer potential, presence of antioxidant activity in *Phyllanthus niruri* are likely attributed to the presence of flavonoids and polyphenols in the extracts. These compounds are known for their ability to scavenge free radicals, which can play a role in the development of ulcers. The study also conducted an acute toxicity evaluation, following OECD guidelines, to determine the safety profile of the extracts. This assessment is crucial when considering the potential use of *Phyllanthus niruri* in clinical settings, as it helps establish a safety margin for therapeutic doses. The findings of this study have important clinical implications. *Phyllanthus niruri's* antiulcer properties could provide an alternative or complementary approach to conventional ulcer treatments, which often have limitations and side effects. Further research, including clinical trials, is warranted to validate these findings in human subjects (12-25).

## 5. Conclusion

The pharmacological evaluation of *Phyllanthus niruri* leaves for antiulcer activity highlights its potential as a natural remedy for the management of peptic ulcers. The observed gastroprotective effects, dose-dependent response, and antioxidant properties suggest that this plant extract may hold promise as a therapeutic option. However, further research is necessary to elucidate the specific mechanisms of action and to establish its safety and efficacy in clinical settings.

**Table 1. Effect of PE and HAL extract of the PNL against ethanol-induced gastric ulcer in rats**

| Group and dose | Ulcer positive animals | Ulcer index | %Ulcer protection |
|---|---|---|---|
| Control (2% w/v gum acacia) | 6 | 7.667±0.03 | - |
| Lansoprazole (8mg/kg) | 1 | 2.01±0.04** | 76.50% |
| Low dose PE (100mg/kg) | 4 | 4.717±0.15** | 23.40% |
| Medium dose PE(200mg/kg) | 3 | 3.137±0.06** | 37.50 % |
| High dose PE(400mg/kg) | 2 | 2.527±0.10** | 59.19 % |
| Low dose HAL (100mg/kg) | 4 | 5.727±0.15** | 22.30% |
| Medium dose HAL(200mg/kg) | 3 | 4.117±0.06** | 40.91 % |
| High dose HAL (400mg/kg) | 2 | 3.547±0.10** | 58.01 % |

**Table 2. Effect of PE and HAL extract of the PNL cold stress induced gastric ulcers in rats.**

| Group and dose | Ulcer positive animals | Ulcer index | %Ulcer protection |
|---|---|---|---|
| Control(2% w/v gum acacia) | 6 | 11.23±0.14 | - |
| Lansoprazole (8mg/kg) | 1 | 1.637±0.03** | 82.00% |
| Low dose PE (100mg/kg) | 5 | 8.612 ± 0.07** | 22.00% |
| Medium dose PE(200mg/kg) | 4 | 7.94 ± 0.16** | 38.00% |
| High dose PE(400mg/kg) | 3 | 5.123 ± 0.06** | 59.17% |
| Low dose HAL (100mg/kg) | 4 | 7.10 ± 0.05** | 35.00% |
| Medium dose HAL(200mg/kg) | 3 | 5.10 ± 0.07** | 54.00% |
| High dose HAL (400mg/kg) | 2 | 3.42 ± 0.07** | 69.00% |

**Lipid Peroxidation Estimation in treated groups in ethanol induced ulcer model in rats**

| Sl. No. | Treatment | Malondialdehyde (MDA) (nm/g gastric tissue) |
|---|---|---|
| **1** | Normal control | 25.05 ± 0.34 |
| **2** | Control | 46.54 ± 0.50 |
| **3.** | Lansoprazole | 30.64 ± 0.48** |
| **4.** | Low dose (PE) (100mg/kg) | 36.38±0.71** |
| **5.** | Medium dose (PE) (200mg/kg) | 35.89 ± 1.03** |
| **6.** | High dose (PE) (400mg/kg) | 31.23±1.09** |
| **7.** | Low dose (HAL) (100mg/kg) | 40.04±1.119** |
| **8.** | Medium Dose (HAL)(200mg/kg) | 33.02±0.75** |
| **9.** | High dose(HAL) (400mg/kg) | 31.22±1.27** |

** P < 0.01 when compared with control

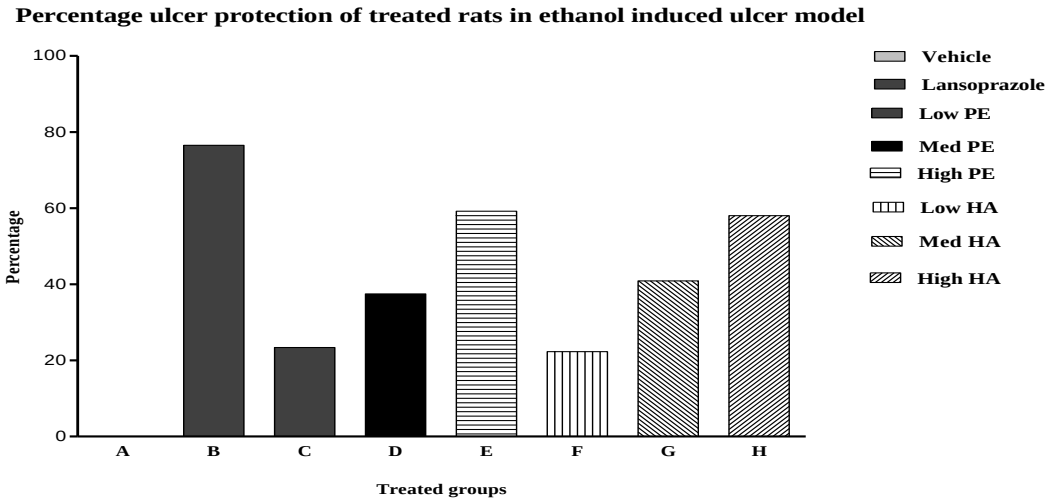



**Fig 01: Percentage Ulcer protection of treated rats in ethanol induced ulcer model**

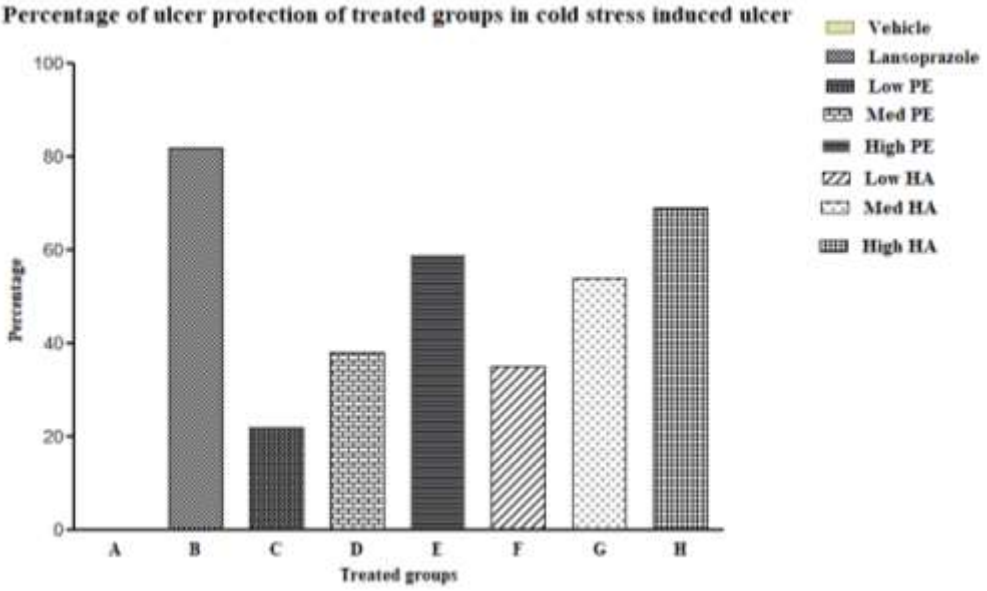



**Fig 02: Percentage Ulcer protection of treated rats in stress induced ulcer model**

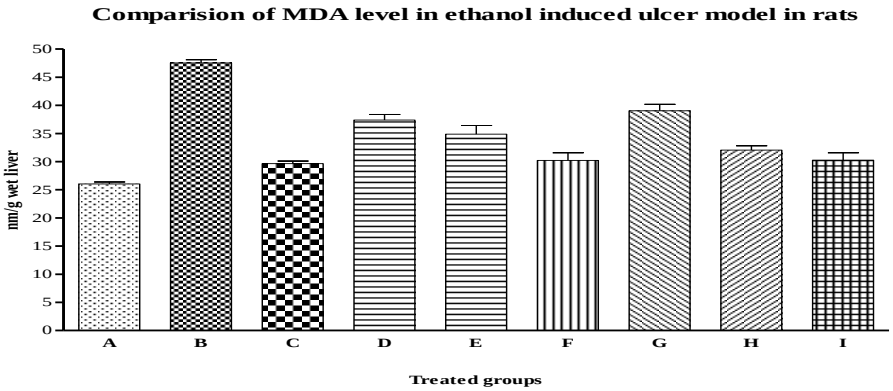



**Fig 03: Comparison of MDA levels in ethanol induced ulcer model in rats.**

**Fig 04: Ulcer pics for various doses**



Control



Toxicant



Lansoprazole



**High dose of HAL**



**High dose of PE**

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**Research Article**

# Exploring the Potent Antidiarrheal Properties of *Capparis Zeylanica* Leaf Extracts

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**Abstract**:

Diarrheal diseases remain a significant global health concern, particularly in regions with limited access to healthcare and safe drinking water. The search for effective, affordable, and sustainable treatments for diarrhea continues to be a priority in the field of medical research. *Capparis zeylanica,* a plant widely distributed in tropical and subtropical regions, has been traditionally used for its medicinal properties. This study investigates the Antidiarrheal potential of *Capparis zeylanica* leaf extracts, aiming to provide scientific validation for its traditional use. The present study investigated the potential antidiarrheal effects of methanolic leaf extract derived from *Capparis zeylanica* (Capparidaceae) using a

castor oil-induced diarrhea model and the small intestine transit method in mice. In comparison to loperamide (2 mg/kg/bw), the ethanolic extract of C. zeylanica (administered at doses of 100, 200, and 400 mg/kg body weight) demonstrated a noteworthy reduction in the severity of diarrhea. The level of protection observed in animals treated with the extract and experiencing diarrhea was compared to those treated with castor oil and loperamide. Notably, the antidiarrheal activity exhibited a dose-dependent response. Additionally, when assessed for its impact on intestinal transit, the extract displayed a substantial decrease in intestinal motility. These results indicate that the ethanolic extract effectively mitigated diarrhea in mice, accompanied by a reduction in stool weight. Further investigation into safety profile of these extracts is warranted to support their development as a viable therapeutic option for diarrheal diseases.

**Keywords**: *Capparis zeylanica*, Antidiarrheal, Leaf extracts, enteric pathogens, Traditional medicine

**Introduction**:

Diarrheal diseases remain a significant global public health challenge, particularly in regions with limited access to healthcare resources and safe drinking water. According to the World Health Organization (WHO), diarrhea is a leading cause of morbidity and mortality, particularly among children under five years of age, accounting for approximately 1.6 million deaths annually worldwide (1). In addition to its impact on mortality, diarrhea places a substantial economic burden on affected individuals and healthcare systems (2).

The treatment of diarrhea typically involves rehydration and, in some cases, the use of antimicrobial agents. However, the emergence of antimicrobial resistance and the limited availability of healthcare facilities in resource-constrained settings underscore the importance of exploring alternative, cost-effective, and sustainable approaches to managing this prevalent condition (3,4).

Traditional medicine has long been a source of remedies for various ailments, including diarrhea. In this context, Capparis zeylanica, a plant widely distributed in tropical and subtropical regions, has a history of traditional use for its medicinal properties. While it has

been utilized by local communities for its potential antidiarrheal effects, there is a paucity of scientific evidence validating its efficacy (5).

This study aims to bridge the gap between traditional knowledge and scientific validation by investigating the antidiarrheal properties of *Capparis zeylanica* leaf extracts. By employing a multidisciplinary approach that includes in vitro assays against enteric pathogens and in vivo experiments using animal models, we seek to elucidate the potential mechanisms underlying its antidiarrheal effects (6).

This research holds the promise of contributing to the development of affordable and accessible solutions for the management of diarrhea, particularly in regions where diarrhea-related morbidity and mortality rates remain high. The study of traditional medicinal plants like Capparis zeylanica represents a valuable avenue for discovering new therapeutic options and addressing global health challenges (7).

## 2.0 Material and Methods

### 2.1 Plant Material

The fresh leaves of *C. zeylanica* (Capparidaceae), collected at the flowering stage in the month of March and were authenticated by the renowned botanist. A voucher specimen was deposited in the departmental herbarium. Leaves were dried in shade for 25 days and then powdered to get a coarse powder. This powder was stored in air-tight container and used for further successive extraction.

### 2.2 Preparation of Crude Extract

The dried and powdered plant material was Soxhlet's extracted with ethanol. The extraction was carried out for 24 h at room temperature with mild shaking. The extract was filtered and concentrated at 45°C, and the weight of the residue was recorded. The percentage yield of ethanolic extract was found to be 38.40% w/w and was used for further studies.

### 2.3 Animals

Albino mice of either sex weighing between 20-30g were procured from central animal house for experimental purpose. The animals were acclimatized to laboratory conditions for 7 days. The animals were supplied with commercially available standard diet from. Water was allowed *ad libitum* under hygienic conditions. All animal studies were

performed in accordance to guideline of CPCSEA and Institutional Animal Ethical Committee (IAEC) guidelines.

**2.4 Acute Toxicity Study**

The acute toxicity assessment of *Capparis zeylanica* leaf extracts was conducted using albino mice of both sexes, weighing between 20-25 grams, and maintained under standardized conditions. Prior to the experiments, the animals underwent a 3-hour fasting period. They were then administered a single dose of alcoholic leaf extract from C. zeylanica and monitored for mortality over a 48-hour study period, which is considered as a short-term toxicity evaluation. Subsequently, in accordance with the guidelines outlined in OECD No. 425 (Acute Oral Toxicity: Up-and-Down Procedure), the subsequent dosages were determined based on the initial short-term toxicity profile. Specifically, doses equivalent to 1/20, 1/10, and 1/5 of the LD50 (lethal dose for 50% of the tested animals) were selected and categorized as low, medium, and high doses, respectively (8).

**2.5 Castor Oil-induced Diarrhea**

Twenty-four mice underwent an 18-hour fasting period and were subsequently divided into five groups, each comprising six animals. All groups received an oral dose of 0.4 ml of castor oil. Thirty minutes after the administration of castor oil, the first group (referred to as the control group) was given a vehicle solution consisting of 0.5% Tween 80 in distilled water. The second group was administered the reference drug loperamide at a dosage of 2 mg/kg body weight. The third, fourth, and fifth groups received doses of 100, 200, and 400 mg/kg body weight, respectively, of the ethanolic extract of *Capparis zeylanica* (ECZ). Subsequently, the mice were individually housed.

To evaluate the severity of diarrhea, assessments were conducted at hourly intervals over a span of 6 hours. The total weight of feces was documented within a 24-hour period and compared to that of the control group. The total number of diarrhea episodes in the control group served as the baseline, representing 100%. The results were then expressed as the percentage of diarrhea inhibition (9,10).

**2.6 Small Intestinal Transit**

The animals were divided into five groups, each comprising six mice. They were orally administered 1 ml of a charcoal meal, consisting of 5% activated charcoal suspended in

physiological saline, 60 minutes after receiving an oral dose of either drugs or a vehicle solution. In specific detail:

- Group I was given physiological saline at a dose of 10 ml/kg.
- Groups II, III, and IV received different doses of the ethanolic extract of *Capparis zeylanica* (ECZ) at 100 mg/kg, 200 mg/kg, and 400 mg/kg, respectively.
- Group V was administered atropine sulfate at a standard dosage of 0.1 mg/kg.

After a 30-minute interval, the animals were humanely euthanized using cervical dislocation. Subsequently, the intestines were carefully removed without stretching and placed lengthwise on moist filter paper. For each animal, the length of the intestine, measured from the pyloric sphincter to the cecum, was recorded. Additionally, the distance traveled by the charcoal meal, expressed as a percentage of the total intestine length, was evaluated. Group means were calculated and compared, and the results were expressed as the percentage of inhibition (11-50).

**2.7 Statistical Analysis**

All the experimental results were expressed as mean± S.E.M. Data were analyzed by analysis of variance (ANOVA) followed by Dunnett's test.

**3.0 Result and Discussion**

The preliminary phytochemical screening of the ethanolic extract of Capparis zeylanica (ECZ) revealed a rich diversity of bioactive compounds, including alkaloids, flavonoids, carbohydrates, glycosides, tannins, terpenoids, and phenols. Notably, the absence of fixed oils and steroids suggests a distinct phytochemical profile for ECZ, consistent with its traditional medicinal use. These phytochemicals are known to possess various biological activities and may contribute to the observed antidiarrheal effects (12, 13). An essential aspect of evaluating the safety of any potential therapeutic agent is the determination of its toxicity. In this study, the median lethal dose (LD50) of ECZ was found to be greater than 2000 mg/kg body weight. This finding suggests that ECZ possesses a relatively low acute toxicity profile, providing a safety margin for potential therapeutic use (14). Castor oil-induced diarrhea is primarily attributed to ricinolic acid, an active metabolite that stimulates peristaltic activity in the small intestine, leading to changes in electrolyte permeability and the release of endogenous prostaglandins (15). The higher dose of

ethanol extract of C. zeylanica demonstrated significant dose-dependent antidiarrheal activity in this study, akin to the standard drug loperamide (2 mg/kg). Several mechanisms could underlie ECZ's antidiarrheal effects. The presence of tannins, sterols, triterpenes, and reducing sugars in ECZ may contribute to its antidiarrheal mechanism of action. Tannins, for instance, have been associated with reducing intestinal secretion, potentially by forming protein tannates that enhance mucosal resistance (16). ECZ may influence intestinal motility, as evidenced by a decrease in intestinal transit observed in the charcoal meal test. A reduction in motility could promote the reabsorption of water and electrolytes from the gastrointestinal tract, contributing to its antidiarrheal efficacy. Loperamide, a standard antidiarrheal drug, is known to regulate gastrointestinal function and slow down transit in the small intestine, which aligns with its observed antidiarrheal effect in this study (17-19). The administration of ECZ at varying doses (100, 200, and 400 mg/kg) resulted in significant protection against diarrhea, with the highest dose (400 mg/kg) demonstrating the most substantial effect. These findings underscore the dose-dependent nature of ECZ's antidiarrheal activity and highlight its potential as a therapeutic agent for managing diarrhea. The observation that ECZ reduced small intestine transit, as indicated by the mean distance traveled by charcoal, suggests that it may enhance the absorption of water and electrolytes from the gastrointestinal tract. Notably, the effect at 400 mg/kg was comparable to that of the standard drug atropine sulfate, a known regulator of intestinal motility. In conclusion, this study provides compelling evidence of the pharmacologically active substances within *Capparis zeylanica* responsible for its antidiarrheal properties.

**Table 1: Effect of ECZ on castor oil-induced diarrhea**

| Treatment (Oral) | Dose | Weight of stool | % Protection |
|---|---|---|---|
| **Control** | 2 ml/kg | 1.178±0.442* | - |
| **Standard** | 2 mg/kg | 0.289±0.274** | 77.34 |
| **ECZ** | 100 mg/kg | 0.498±0.0254** | 55.83 |
| **ECZ** | 200 mg/kg | 0.312±0.0124** | 68.12 |
| **ECZ** | 400 mg/kg | 0.411±0.0244** | 71.23 |

**P<0.01 and *P<0.05 statistically (Mean±Sem) significant from control group.

**Table 2: Effect of ECZ on small intestinal transit method**

| Treatment (Oral) | Dose | Mean distance travelled by charcoal as % total length of small intestine (cm) | % Reduction |
|---|---|---|---|
| **Control** | 2 ml/kg | 85.24±1.872 | - |
| **Standard** | 0.1 mg/kg | 14.267±2.454 | 80.45 |
| **ECZ** | 100 mg/kg | 38.57±1.254* | 51.63 |
| **ECZ** | 200 mg/kg | 32.485±1.012* | 63.21 |
| **ECZ** | 400 mg/kg | 22.512±1.134* | 74.08 |

**P<0.01 and *P<0.05 statistically (Mean±Sem) significant from control group.

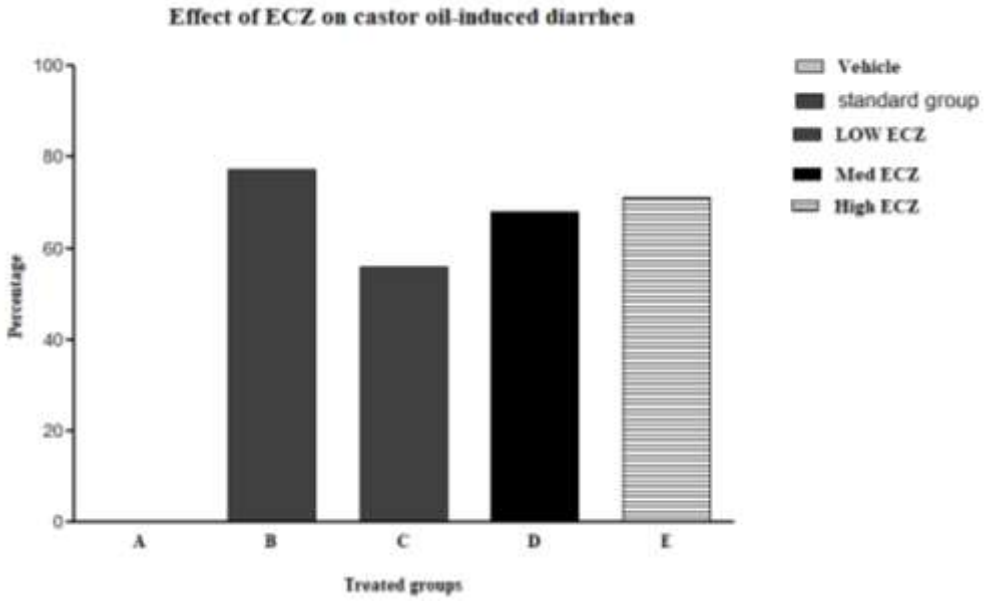



**Fig 01: Effect of ECZ on castor oil induced diarrhea**

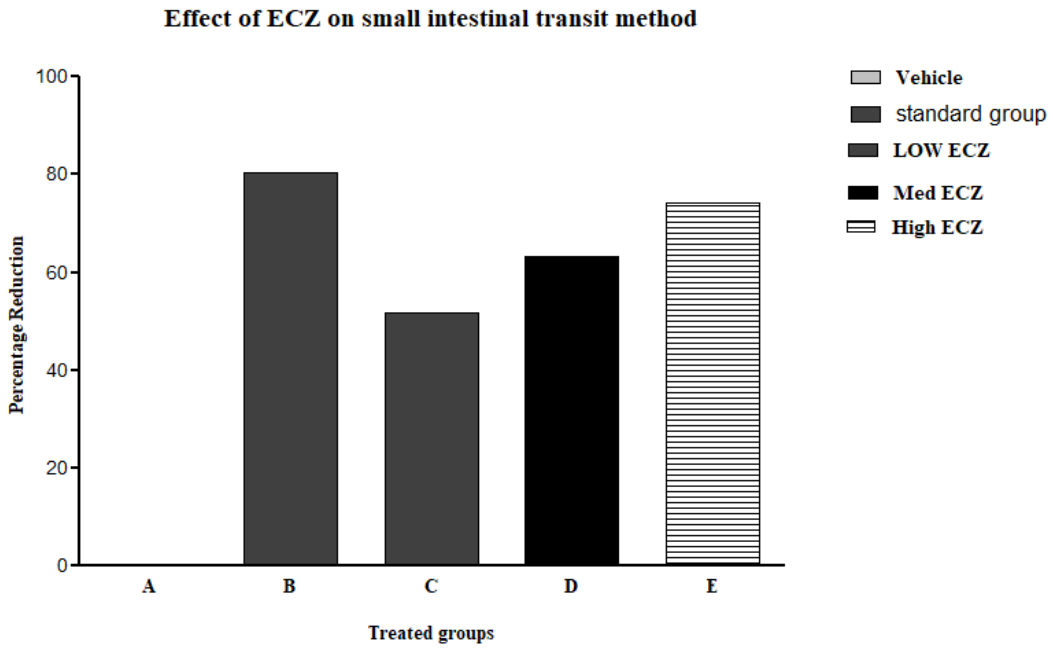



**Fig 02: Effect of ECZ on small intestine transit method**

**4.0 Conclusion:** These findings support its traditional use as an effective antidiarrheal remedy. Further research is warranted to isolate and characterize the specific molecules responsible for ECZ's antidiarrheal activity, potentially paving the way for the development of novel therapeutic agents for diarrheal conditions.

**5.0 Source of Support:** Nil

**6.0 Conflict of Interest:** Nil.

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**REVIEW ARTICLE**

# Unlocking the Potential of *In-silico* Approaches: Drug Development and Vaccine Design

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**ABSTRACT**

Unmatched in its field, bioinformatics combines several academic fields such as statistics, computer science, mathematics, and biology to create state-of-the-art techniques for biological data retrieval, storage, and analysis that lead to a thorough understanding of the biological world. Countless options currently accessible in field of living sciences by the expansion of *in-silico* biology. Paradigm of life sciences has changed as a result of *in-silico* technologies, which offer researchers a valuable and affordable way to focus on *in-silico* techniques like homology modeling, epitope prediction, and molecular docking, which have impacted drug discovery and vaccine design. These techniques also provide previously unheard-of predictions and insights.

**Keywords:** β-cell Prediction, Drug development, Vaccine design, Infertility, *In-silico* approaches.

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## INTRODUCTION

Researchers encounter new challenges every day, which pushes them to become more imaginative and practical. With its great diversification, biology currently includes several subfields, including microbiology, genetics, physiology, ecology, and others. It appears that scientists produce vast amounts of data regarding the genome, biomolecules, organisms, their interface, and progression. As a result, there is a budding necessitate for computational methods to gather, interpret, and analyze the data, which can occasionally be rather complex. Managing and analyzing vast volumes of biological data has become increasingly difficult, but the rapidly developing discipline of computational biology, or bioinformatics, has helped.[1] An interdisciplinary field-bioinformatics coalesce computer science, statistics, mathematics, biology, and other fields to create techniques for archiving, retrieving, and analyzing biological record.[2] "*In-silico*" is an alternate abbreviation that is much more widely recognized and has been used for 50 years.[3] "*In-silico*" approaches are forecasts that rely on computer models, as the term "*in-silico*" derives from the word "silicon," which is related to computers. American physical chemist Margaret Dayhoff (1925–1983) was a trailblazer in the application of computational techniques. Her contributions to this discipline have been so great that she has been referred to as the parent of bioinformatics" by David J. Lipman, ex-director of NCBI.[4] The integration of *in-silico* tools with genomic, proteomic, metabolomic, and transcriptomic data presents significant opportunities for comprehending diverse biological mechanisms and creating novel strategies for identifying, forecasting, and managing illnesses like cancer and neurological conditions, all while mitigating adverse consequences.[5] High-throughput computer systems have replaced traditional biological techniques since the development of *in-silico* technology, mostly because to cost, time, and energy savings. Rapid technological advancements led to the emergence of this subject and had a profound effect on proteomics, which is today regarded as the core of laboratories. These advancements also made it possible for researchers to quantify the genomes of many different animals.[6] Researchers need quick answers in situations like COVID-19, and bioinformatics is essential to achieving this goal and laying the groundwork that is required.[7] Moreover, informaticians

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have significantly aided the Human Genome Project and other omics studies by computerizing the research process.[8] The historical procedure for creating a novel medication was a protracted and challenging endeavor, typically requiring over $1.8 billion in expenses and more than a decade from the moment a potential drug candidate was pinpointed to the conclusion of clinical trials. The assessment of the potential drug candidate's toxicity and adverse effects primarily involved *in-vivo* and *in-vitro* techniques.[9] Conversely, the development of *in-silico* has reduced scale, time, and cost concerns while simultaneously improving the efficiency and accuracy of drug target and therapeutic medicine identification. It has also lessened the workload associated with evaluating a drug candidate's possible toxicity in animals.[10] Proteomics research now has new directions thanks to bioinformatics. The databases' proteomic and genomic data have given medical researchers the knowledge they need to understand metabolic pathways. Protein structures were previously ascertained experimentally using nuclear magnetic resonance (NMR) or X-ray crystallography,[11] which was not practical for all protein samples; however, today, target protein 3D structures can be inferred using computational structure prediction techniques like comparative modeling[12] or ab-initio modeling. This review requests the databases and *in-silico* methods created for drug and vaccine design. Additionally, it highlights the use of computational tools to clarify antigen sharing between humans and pathogens.

## Common Approaches Involved in *In-silico*

### *Sequence database*

In light of the massive amount of data generated, its organization and storage become the utmost necessity to which databases were constructed.[13] High-throughput sequencing techniques led to a rapid cohort of extensive genomic statistics. To make this information publicly available, numerous databases have been created worldwide. A biological sequence database is an extensive repository of information pertaining to biomolecules, including proteins and nucleic acids, wherein each biomolecule is identified by a distinct identifier. This review delves into the intricacies of protein databases, highlighting their significance as an authoritative means for exploration and understanding of the complex and dynamic nature of proteins.

### *Protein databases*

Protein sequence databases are used as a storage and organization system for data pertaining to proteins. The first protein sequence catalog was the protein information resource, which was founded in 1984 by NBRF.[14]

Studies of protein diversity and function in a variety of organisms and biological processes are made easier by the UniProt database system. Over 227 million sequences are included in the UniProtKB database in UniProt release 2022-2023.[15] A collection of reviewed protein sequences and annotations is called the UniProt Knowledgebase (UniProtKB) (UniProtKB/Switzess-Prot). Each protein entry in this has a link to an overview of experimentally validated or computationally envisaged valuable information added by the connoisseur biocuration team.

The Protein Data Bank (PDB) is a globally acknowledged source of structural information about biological macromolecules. Researchers can submit data from X-ray crystallography and NMR spectroscopy to PDB, which houses these types of data and offers a variety of tools for protein analysis, visualization, and sequencing.[16]

### *Homology modeling*

In recent years, NMR, X-ray crystallography, and cryo-electron microscopy (cryo-EM) have all gained prominence as crucial instruments for examining the three-dimensional configurations of proteins. While the field of proteomics has been advancing swiftly, there remains a substantial discrepancy between the quantity of experimentally ascertained protein three-dimensional structures and the known protein sequences. To bridge this gap, homology modeling has surfaced as a widely adopted alternative method for predicting protein structures.[17]

Utilizing preceding facts from structural resemblance amid other proteins, homology modeling, also referred to as comparative protein modeling, is a computational method for generating 3D structures of proteins from their amino acid sequences.[18] Using tools like BLAST, profile-profile alignments, and Hidden Markov Models (HMMs), the eligible templates are first found through sequence alignment in comparative modeling.[19] Programs like CLUSTAL W, CLUSTAL Omega, and MUSCLE can be used to obtain multiple sequence alignments.[20] One of the following four approaches can be used to create the 3D model: segment matching or coordinate reconstruction, artificial co-evolution, comparative modeling by spatial constraints, and modeling by assembly of rigid bodies.[21] An essential step in determining the functional stability and creation of the functional ligand binding sites is loop modeling.[22] It is carried out using conformational search techniques or database search techniques. Using rotamer libraries and scoring functions and software like SCRWL, OPUS-Rota-2, and FASPR, side chains are added to the model in the next step. The last stage was to improve the protein structure's quality. This phase, referred to as "model optimization," improves the final model's quality by removing unfavorable non-bonded interactions and optimizing bond geometry.[23,24] To prevent steric collisions between atoms, energy minimization techniques such as CHARMM, AMBER, and GROMOS are employed; molecular dynamics and Monte Carlo simulations can be used for additional optimization.[25] By examining the 3D conformations and statistical potentials of the model, programs like VERIFY3D and PROSAII assess the spatial accuracy of the model. Protein structural modeling has advanced significantly in recent years, offering biologists numerous opportunities to further their research. Scientists can now overcome production challenges with informed decision-making thanks to homology modeling. Besides, homology modeling has emerged as a functional tool in a meadow of realistic drug design, chiefly for high-throughput *in-silico*

assortment and recreation approaches. This has created new opportunities for the field's researchers to accomplish their objectives more quickly and successfully.[26]

*Molecular docking*

Here, we delve into the computational analysis of interactions between two molecules. Specifically, one molecule serves as a small ligand, while the other acts as a macromolecular protein receptor. Molecular docking stands out as a preeminent computational structure-based approach for drug design, a methodology that gained prominence since its inception in the early 1980s.[27] Through the characterization of the behavior of ligand molecules within the binding site of target proteins, the molecular docking approach plays a crucial role in enhancing our comprehension of fundamental biochemical processes. This methodology facilitates the exploration of atomic-level interactions between the ligand and the protein, thereby contributing valuable insights to the field.[28] A systematic process takes place in molecular docking, beginning with the crucial step of protein formulation**.** This involves determining the target structure experimentally using Molecular docking is a methodical process that starts with the important step of protein formulation. In order to do this, the target structure must be determined experimentally using methods like X-ray crystallography or NMR. With differing degrees of accuracy, homology models can also be utilized in the absence of this data. The 3D structure is obtained from the PDB and pre-processed for stability and missing residues.[29,30] Ligands can be obtained from PUB Chem and ZINC databases, but if their 3D coordinates are unavailable, they can be created using tools based on their 2D structures such as Avogadro, Chem-Sketch or Chem-Draw. Docking, the last phase looks at how the ligand and protein interact. To determine the optimal ligand pose, search algorithms and scoring functions are needed. An RMSD of less than two angstroms indicates a successful docking prediction. The accuracy of the docking prediction is evaluated using this calculation. Ki values or inhibition constants can be used to assess the ligand's potency To put it briefly, molecular docking is an effective technique that leads to new avenues for biological research and gives scientists a better understanding of the molecular interactions at the core of life[29]. Using programs like MolDock or DoGSiteScorer, potential binding sites are found through active site prediction in the following stage.[31]

## Exploring the Unrivalled Contributions of *In-silico* in Drug Development, and Vaccine Designing

*Drug discovery*

The primary objective of the drug design and development process is to identify new compounds that are both safe and efficacious. Historically, drug discovery was a challenging, expensive, and often inefficient undertaking. However, recent advancements, particularly in technologies such as *in-silico* drug design, have made the process more attainable. The evolution of the drug discovery process aligns with contemporary trends, benefiting from enhanced specificity and efficiency in databases developed through the integration of big data and advancements in information technology.[32] The most popular *in-silico* methods in the drug development process are homology modeling, molecular simulations, molecular docking, and epitope prediction. Using these techniques can help save time and resources by constructing precise models of the target molecule and identifying the optimal binding orientation of a drug candidate. Antimicrobial compound structures were taken from Pubchem, and MRSA protein structures were taken from the RGCB PDB database. Protohypericin, galangin, berberine, and berbamine were found to be potent compounds with strong binding affinities to the targeted proteins through docking experiments. Promising inhibition of significant *Staphylococcus aureus* proteins was demonstrated by *Beberis vulgaris*, *Hibiscus sabdariffa*, *Chelidonium majus*, *Mahonia aquifolium*, *Hypericum perforatum*, and *Rheum ribes*. These substances have the potential to be antibiotics because they have few side effects on human health. Since it was established that COVID-19 infection could still occur in people even in the presence of the vaccine.[33] To find inhibitors of SARS-CoV-2 that aim at particular protein targets. Thirteen putative protein targets were found after a thorough literature review. After 501 medicinal phytochemicals were screened, 26 compounds with remarkable anti-SARS-CoV-2 efficacy were found. Notably, Gmelina arborea's 4,8-dihydroxysesamin and arboreal showed encouraging activity against a variety of targets. Their higher affinity for the nucleocapsid target was revealed through comparative analysis with established medications. All things considered, these substances show great promise in blocking SARS-CoV-2.[34]

*Vaccine designing*

Infectious organisms were partially inactivated or attenuated to create conventional vaccinations. Although this method was advantageous at the time, it took more than five to fifteen years and resulted in adverse effects like fever and hypersensitivity. One solution to the problems with conventional vaccination methods has been proposed: the development of novel vaccine candidates.[35] The field of computational *in-silico* immunoinformatics aids in the creation of novel vaccines. Advances in immunology and computational biology for the identification of immunogenic epitopes can trigger an immune response, have greatly aided in the design and development of vaccines. Using *in-silico* methods to predict a vaccine candidate's potential efficacy in advance, such as molecular simulation and epitope prediction, can expedite the vaccine development process. Epitope prediction has become crucial in identifying the epitopes that can activate T and B cell responses.[36,37] An epitope, also known as an antigenic determinant, is an exposed surface area of an antigen that, upon binding an antibody, elicits an immune response. Specific antibodies (Abs) recognize antigenic determinants, which are discrete regions of an antigen (Ag).[38]

*Epitope prediction for B cells*

B-cell epitopes refer to clusters of amino acids on the surface of proteins that are recognized by B-cell receptors or secreted

antibodies, eliciting a humoral or cellular immune response. The intricate spatial arrangement of B-cell epitopes can be broadly categorized into two groups: continuous (linear or sequential) and discontinuous (nonlinear or conformational). Conformational B-cell epitopes consist of non-sequential amino acid residues in the protein's main structure that fold in nearby regions. On the other hand, linear epitopes, also known as continuous epitopes, are short peptide segments of an antigen composed of successive amino acid residues, typically not exceeding 15 amino acids in length.[39-41]

*T-Cell epitope prediction*

A vital immunology endeavor in which the ultimate goal is to determine peptides within an antigen that is most concise and capable of eliciting a strong response from CD-4 or CD-8 T-cells.[42]

By using a logical design that saves time and money, *In-silico* also aids in the development of vaccines. These computer simulations are being used to test antiviral small compounds and peptides due to their higher selectivity and a decreased tendency to elicit unwanted immune responses. Computational methods were employed to create a vaccine against drug-resistant *Mycobacterium tuberculosis* (Mtb) strains. They concentrated on a multi-epitope subunit vaccine made of Mtb antigens that have been experimentally verified.[43] IEDB was used to predict the epitopes on B and T-cells, and bioinformatics techniques were used to refine and validate the 3D structure. To improve the vaccine, docking with TLR-3 was carried out and a number of factors were taken into account, such as molecular docking scores, physiochemical properties, allergenicity, antigenicity, and solubility. *In-vitro* positive immune cell responses were shown by *in-silico* immune simulations. According to the research, this multi-epitope vaccine is a promising candidate for a tuberculosis vaccine because it may trigger both humoral and cellular immune reactions sought to create an *in-silico* vaccine based on epitopes to protect against the fungal infection aspergillosis. Predicted B and T cell epitopes were used in molecular docking studies with corresponding receptors. Linear B cell epitopes were identified from two short peptide chains based on their physicochemical properties.[44,45] The most likely T cell epitope was determined to be the peptide sequence 221LDLFQNAFTQLADVS235, which together with the peptide-MHC, T cell receptor, and CD4 molecule complex formed a stable dock structure. To find out if these proposed epitopes are suitable for peptide-based aspergillosis vaccinations, more experimental validation is needed. Use of different immunoinformatics skills to develop a multi-epitope vaccine against *Legionella pneumophila*.[46-50]

## CONCLUSION

This review describes *in-silico* approaches in drug development and vaccine design; it mentions T and B cells epitope predictions, molecular docking and sequence database.

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