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Chitosan a natural anti-inflammatory and wound healing agent: A brief update

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ABSTRACT: Inflammation is a complex physiological response that serves as a critical component in the pathogenesis of various diseases. Over the years, chitosan, a natural polysaccharide sourced from chitin, has gained significant attention as a prospective anti-inflammatory agent. This brief review aims to summarize the existing knowledge about chitosan's anti-inflammatory effects and mechanisms. It discusses *in vitro* and *in vivo* studies on chitosan's impact on inflammatory markers, immune responses, and cellular signaling pathways. Additionally, it presents an overview of the different formulations and delivery systems of chitosan utilized in preclinical and clinical studies. The findings suggest that chitosan exhibits promising anti-inflammatory effects by modulating pro-inflammatory mediators, inhibiting inflammatory enzymes, and regulating immune cell functions. Moreover, the biocompatibility, biodegradability, and low toxicity of chitosan make it a promising candidate for therapeutic applications. However, additional investigation is necessary to clarify the exact mechanisms that explain its anti-inflammatory activity and enhance its therapeutic potential. Overall, this review highlights the chemistry, applications of chitosan in biomedical fields, and the utilization of chitosan as an anti-inflammatory agent in drug delivery systems, with a growing body of evidence supporting the potential of chitosan as a valuable anti-inflammatory agent, paving the way for future investigations and the development of novel therapeutic interventions.

1. INTRODUCTION

Chitin is a multipurpose biopolymer with diverse utilizations in many fields. It is the main structural element of yeast and fungal cell walls, as well as the exoskeletons of crabs and prawns. Every year, around 1500 tons of chitin are produced worldwide (Kurita, 1998). Chitin is not easily soluble in most solvents, oftentimes it is converted to chitosan, a more deacetylated derivative (Azuma et al., 2015) (Figure 1). Chitosan is generally considered to be chitin that has been deacetylated by 70% or more. The primary functional groups in chitosan, amino groups, are created when the acetamide groups in chitin undergo deacetylation. Alkaline deacetylation is a common method for converting chitin to chitosan (Y. Zhang et al., 2005).

Chitosan is an amino polysaccharide abundant in nature which consists of β-(1 $\rightarrow$ 4)-linked 2-acetamido-2-deoxy-D-glucopyranose and 2-amino-2-deoxy-D- glucopyranose units (Ahmed & Ikram, 2016). Research advancements have shown that chitosan may be used as an anti-inflammatory agent and because of its biocompatibility, non-toxicity and versatility, the usage of chitosan is favoured in several industrial sectors regardless of their poor solubility (Joseph et al., 2021). Chitosan dissolves in weak aqueous solutions of acetic, lactic, malic, formic, and succinic acids, as shown in several studies. Chitosan is a polycationic molecule at pH below 6, which means it has a positive charge. This positive charge facilitates its rapid interaction with negatively charged molecules, including phospholipids, proteins, anionic polysaccharides, fatty acids, and bile acids (Ahmed & Ikram, 2016).

Three different types of reactive groups are present in chitosan: a primary hydroxyl group at position C-3, a primary amine group at position C-2 of the glucosamine residue, and a primary and secondary hydroxyl group at position C-6. The most crucial functional component for chitosan's biological action is the main amine group (Suryeon, 2018) (Figure 2).

The physicochemical makeup of chitosan, which includes its molecular weight, moisture content, and degree of acetylation, are closely related to its biological properties (M. Zhang et al., 2022). Chitosan provides a diverge range of applications (Figure 3), including (Kumar, 2000):

- Chemistry: Chitosan can be used to develop new bioplastics and other biomaterials.
- Biochemistry: Chitosan can be used to purify proteins and enzymes,and to develop new biocompatible materials.

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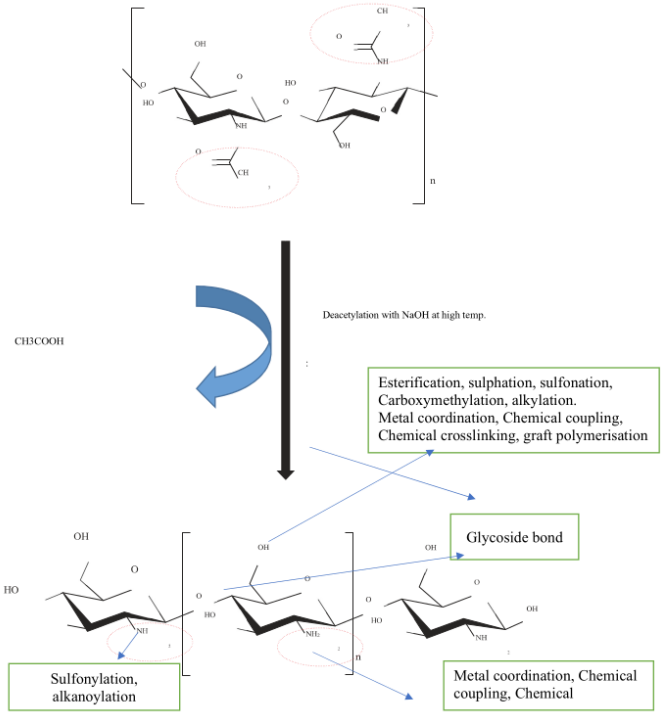

Figure 1. Chitin deacetylation with alkali.

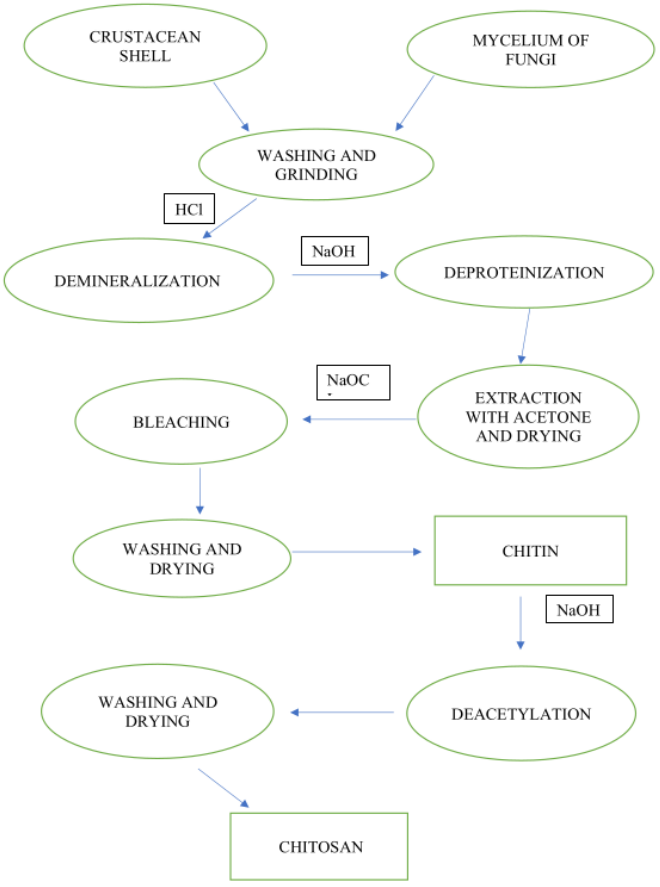

Figure 2. Preparation of chitin and chitosan from raw material(Sandeep et al., 2013).

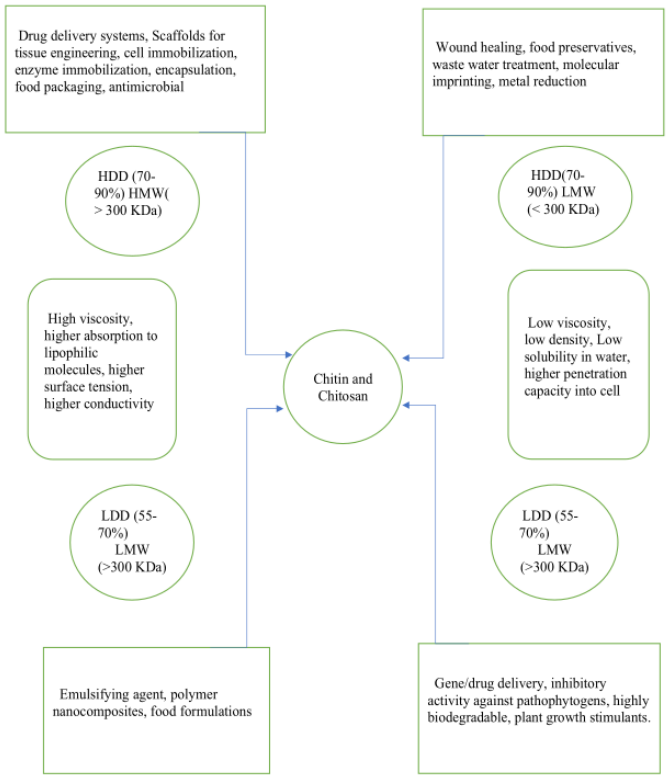

Figure 3. Different properties of Chitosan and its applications.

- Microbiology: It is possible to utilise chitosan to stop the growth of fungus and bacteria.
- Polymer engineering: Chitosan can be utilized to develop new drug delivery systems and wound healing dressings.
- Pharmacy: Chitosan can be used for developing new drugs and vaccines.
- Medicine: Chitosan can be employed for a range of ailments including inflammation, infection, and cancer.
- Material sciences: Chitosan can be used to develop new materials for food packaging, water filtration, and tissue engineering.

Chitosan presents a broad spectrum of potential applications in the biomedical field and is acknowledged as a novel material in areas like drug delivery systems (Figure 4), wound healing, antimicrobial properties, fat binding, hemostatic action, and its potential to lower cholesterol levels (Table 1). This recognition is supported by numerous recent research studies. Chitosan's antibacterial properties are due to its many alkaline amino groups, which are positively charged in acidic conditions. This positive charge disrupts and destroys the membranes of bacterial cells, preventing bacteria from infecting wounds (Minagawa et al., 2007).

Chitosan plays various roles, serving as a food supplement, contributing to moisture in cosmetic products, and, in recent times, emerging as a pharmaceutical component for the creation of biomedical solutions, especially as an antibiotic in clinical applications. It is also being explored as a potential medium for the delivery of radiopharmaceuticals, genes, and peptides.

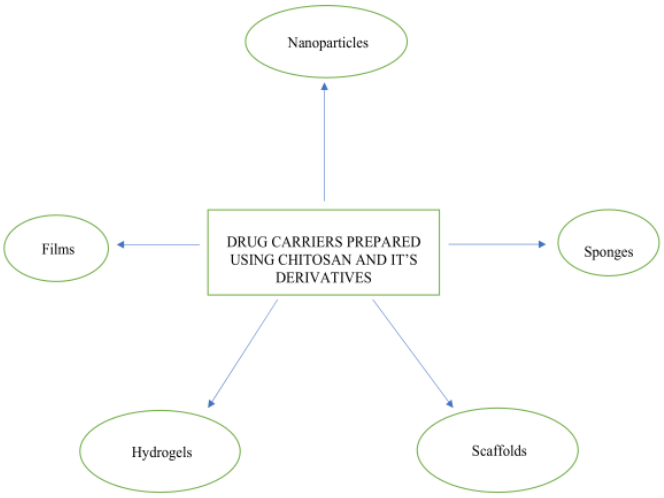

Figure 4. Chitosan-derived drug delivery systems.

This substance, characterized by its weakly basic nature, doesn't readily dissolve in aqueous or typical organic solvents. However, it can disperse in slightly acidic aqueous solutions at pH of approximately 6.5. Conversely, in alkaline conditions or when mixed with polyanions, it undergoes precipitation and forms a gel (Fini & Orienti, 2003).

Chitosan/ chitin breaks down into shorter molecules called NACOS (N-acetyl-d-glucosamine oligomers) and COS (d-glucosamine oligomers) via acid, physical means, or enzymes. These molecules dissolve easily in water because they are smaller and have fewer bonds to break. Researchers prefer to use chitosan oligosaccharides (COS) because they are less viscous and more soluble than chitosan at neutral pH (Choi et al., 2016).

2. CHITIN/ CHITOSAN CHEMISTRY

2.1. Mucoadhesiveness

Due to its natural cationic character and weaker hydrophobic interactions than anionic polymeric carbomers, chitosan is mucoadhesive. As opposed to the relatively weak mucus gel layers, the sustainable mucoadhesive feature enables significant cohesive/adhesive bonds within polymeric matrix. Combining chitosan with other negatively charged molecules, such as inorganic or organic ionic medications, can improve the chemical, biological, or physical properties of chitosan (Dongre, 2019). Cationic substructures that confer ionic interactive mucoadhesion are partially responsible for some key modifications in its skeleton. When combined with polyanionic carbomer, such mucoadhesive chitosan does not achieve oral bioavailability (Kumar et al., 2004).

2.1.1 Trimethylation of NH2 functionality

- Chitosan has amino groups (NH2 functionality) which can be modified by adding three methyl groups (trimethylation).
- This chemical modification alters the structure of chitosan, enhancing its cationic (positively charged) properties.

2.1.2 PEGylated derivatization or immobilizing thiol groups

- PEGylation involves attaching polyethylene glycol (PEG) chains to chitosan. PEGylation can modify the surface properties of chitosan, impacting its interactions with biological tissues.
- Immobilizing thiol groups involves attaching sulfur-containing groups to chitosan. Thiol groups can form bonds with other molecules, influencing the overall properties of chitosan.

The combined effect of these modifications is an increase in the cationic nature of chitosan, making it more positively charged. This enhanced cationicity can improve its interaction with negatively charged mucosal surfaces (mucoadhesiveness). Overall, these modifications tailor chitosan for better performance in applications like drug delivery or biomedical formulations (Bernkop-Schnürch & Dünnhaupt, 2012; Kavitha et al., 2011). Overall, chitosan is a versatile mucoadhesive polymer that can be altered to improve its qualities for versatile utilization.

2.2. Permeation characters

Chitosan has significant cationic properties and NH_2/OH functionality, which facilitates the structural reconfiguration of tight junction-associated proteins and increases permeability. Rationally chosen levels of deacetylation and the molecular weight of natural chitosan were discovered to govern improved penetration and lowered toxicity in addition to somewhat increased epithelial permeability (Dongre, 2019).

Chemical modification of chitosan leads to the generation of various derivatives, including quaternized chitosan, thiolated chitosan, carboxylated chitosan, amphiphilic chitosan, chitosan with chelating agents, PEGylated chitosan, and lactose-modified chitosan. The primary amine groups (-NH2) present in chitosan serve as reaction sites for diverse chemical modifications, enabling the attainment of different pharmaceutical applications (Mohammed et al., 2017). These modifications involve reactions with sulfates, citrates, and phosphates, thereby enhancing stability and drug encapsulation efficiency (Lodi et al., 2021).

For instance, to address the solubility of chitosan in intestinal media, N-trimethyl chitosan chloride (TMC), a quaternized chitosan, has been synthesized (Ghume, V.K., 2020). The two variants of TMC, namely TMC 40 and TMC 60, have demonstrated an improvement in the intestinal permeation of hydrophilic macromolecular drugs. Chitosan is simple to combine with other permeability enhancer doping drugs, which can result in a synergistic effective phenomenon that causes activity to increase by four times (Kumar et al., 2004). For the successful drug administration of various biomaterials/drugs in cancer therapy and colon disorders, several chitosan blends/composites are used. N-trimethylated chitosan derivatives combined with polyethylene glycol (PEG) are utilized to create hydrogels for nasal drug delivery, with consideration given to the inherent molecular weight of chitosan, categorized as low, medium, or high. Notably,

the high or moderate molecular weight chitosan, when N-trimethylated and blended with PEG, exhibits a narrower sol-gel transition range at body temperature, in addition to its strong mucoadhesive properties. These chitosan hydrogel formulations offer several advantages, including rapid sol-gel transition at room temperature, favorable pharmacokinetics, rheological properties, and mucoadhesion. They enable controlled and sustained drug delivery, promote stability, enhance effectiveness, and exhibit low toxicity. Within these chitosan-nanostructured frameworks, modifications involving the hydroxyl and primary amino functionalities lead to biological and physicochemical cross-linking within the matrix. The formation of precipitates occurs due to the merging of chitosan droplets with alkaline solutions, while stable droplets are formed through emulsion and high-speed stirring, resulting from random collisions. An additional technique involves the use of a reverse micellar medium to produce ultrafine chitosan nanoparticles with narrow particle sizes, either 1 or 10 nm, which are highly suitable for efficient drug delivery. By utilizing surfactants dispersed in an organic medium to generate reverse micelles, this systematic encapsulation approach can be employed to incorporate various conjugates into the chitosan matrix, producing noteworthy nanoparticles for macromolecule distribution, with promising prospects in research and development (Kavitha et al., 2011; Wu et al., 2010).

Thiolated derivatives of chitosan, such as chitosan-thioglycolic acid, chitosan-cysteine, chitosan-glutathione, and chitosan-thioethylamidine, are currently in use. NPs based on TMC-cysteine have demonstrated significantly enhanced mucoadhesion and permeation compared to TMC NPs. The incorporation of poly (methyl methacrylate) through grafting carboxylated chitosan has been employed to achieve pH-sensitive properties (Hanbali et al., 2019).

For the treatment of cutaneous leishmaniasis, amphotericin B-loaded chitosan nanoparticles were developed. Two variants with distinct electrical properties were prepared using positively charged sodium tripolyphosphate (TPP) and negatively charged dextran sulfate as crosslinkers. Both types exhibited high *in vitro* activity against Leishmania amastigotes. Interestingly, amphotericin B in aqueous solution struggled to penetrate the skin. When applied to isolated mouse skin, both types of AmB-loaded chitosan nanoparticles facilitated a slow and limited penetration of AmB, achieving osmotic balance after approximately 20 hours. This suggests that chitosan nanoparticles can enhance the *in vitro* skin permeation of amphotericin B. Furthermore, the inclusion of nanoparticles in chitosan matrices was found to delay drug release, as highlighted by Riezk et al. (2020).

Tacrolimus-loaded chitosan nanoparticles were formulated by Salma et al. using ion gelation technology for the purpose of treating psoriasis. The *in vitro* skin permeation study was conducted over a 24-hour period. After this duration, the permeability of tacrolimus in the chitosan nanoparticles was found to be 24%, in contrast to the 61% permeability observed with tacrolimus cream. This indicates a significant ability of the chitosan nanoparticles to effectively delay the release of tacrolimus, thereby reducing the systemic toxicity of the drug. Furthermore, the skin deposition rate after 24 hours for tacrolimus cream was 11.4%, whereas the tacrolimus chitosan nanoparticles exhibited a considerably higher rate of 75%. This demonstrates a notable advantage in delivering tacrolimus to the skin, the intended target site for treating psoriasis, as reported by Fereig et al. (2021).

Atransdermal emulsion coated with chitosan containing 5-fluorouracil exhibited favorable skin permeation characteristics when compared to the 5-fluorouracil solution. The enhanced permeation was attributed to the fluidization of the stratum corneum by chitosan and surfactants in the emulsion, as previously described by Khan et al. (2021).

An investigation on impact of chitosan coating on the skin permeation properties of clotrimazole microemulsion conducted and the study involved measuring drug retention in rat skin after 8 hours of transdermal permeation. Results indicated that the chitosan-coated clotrimazole microemulsion exhibited significantly higher drug retention in the skin compared to the control clotrimazole microemulsion ($p < 0.05$), according to Kumari and Kesavan (2017).

Trombino et al. conducted research on combining cyclosporin A with chitosan carboxylate through an amidation reaction to create a prodrug. This prodrug was uniformly dispersed in a chitosan-based polymer membrane for the treatment of breast cancer. Skin permeation experiments on porcine skin demonstrated that the model drug coumarin-6 could penetrate into the dermis, indicating penetration beyond the surface and into deeper layers of the skin, according to Trombino et al. (2021).

Unlike all other biodegradable polymers with a specified entry in a pharmacopoeia, chitosan stands out as the sole polymer displaying a cationic nature, setting it apart from the rest (Bernkop-Schnürch & Dünnhaupt, 2012).

2.3. INFLAMMATION

Inflammation represents the body's initial defensive response to infection or injury in a specific tissue region, involving a distinct group of immune and inflammatory cells. Its primary goal is to restore the structural and functional well-being of the affected area following exposure to adverse stimuli (Punchard et al., 2004).

Historically, inflammation was defined based on visual observations, characterized by five cardinal signs: redness (rubor), swelling (tumour), heat (calor), pain (dolor), and loss of function (functio laesa) (Schmid-Schönbein, 2006) .

The term "anti-inflammatory" pertains to drugs or therapeutic methods aimed at reducing inflammation. Unlike opioids, which impact the central nervous system, anti-inflammatory medications constitute roughly half of analgesics and work by alleviating both pain and inflammation (Dinarello, 2010).

Table 1
Specific chitosan formulations or composites employed for regulated drug release.

Chitosan-based formulations	Purpose	Applications	Reference
Chitosan-based nanogels	Optical based pH-monitoring	Hybrid nanogels that are obtained from chitosan display non-reversible pH reactivity. Additionally, quantum dots composed of chitosan-nanogel are utilized in this context.	Wu et al. (2010)
Chitosan-ZDV (Zidovudine) composite	Prevents the degradation of Zidovudine in human plasma, ensuring its long-term stability.	The composite remains in the kidney for a more extended period (shelf life) compared to the liver, heart, spleen, lung, and brain.	Hasanjani and Zarei (2021)
Zinc-pectin-chitosan hybrid	Delivery of Resveratrol in colon	The most effective drug release at the colon was achieved using a 1% chitosan preparation with a pectin/drug ratio of 3:1 under pH 1.5 conditions.	Andishmand et al. (2017)
Sodium alginate-chitosan formulation	Administration of drug through vaginal route	A composite of alginate, consisting of chitosan and sodium (in a 1:4 weight ratio), exhibited controlled release of the medication chlorhexidine digluconate.	Abruzzo et al. (2013)
Chitosan-PEM (Polyelectrolyte multilayer) vascular patches	Drug delivery for vascular regeneration	Improved hemocompatibility, enhanced anti-platelet adhesion ability, prolonged *in vitro* coagulation time, and decreased hemolysis rate of Heparin	Sun et al. (2022)
Cyclosporin A-chitosan hybrid	Extraocular and transdermal delivery of drug	Improved therapeutic efficacy of challenging drugs employed for extraocular and skin diseases.	Başaran et al. (2014)
Chitosan nanospheres of 5-fluorouracil	Delivery of 5-fluorouracil for cancer therapy	These stable nanoparticles of chitosan, at a nanoscale, have the ability to transport medications to tumor cells and encapsulate them within those cells.	Dongsar et al. (2023)
Chitosan- TPP (Tripolyphosphate) composite	Administration of Insulin for diabetes management	Chitosan enhances bioavailability and, as a result of reduced intestinal absorption, leads to lower blood sugar levels.	Prabahar et al. (2020)
Chitosan- DNA nanomatrix	Carrier of enclosed plasma DNA	Chitosan nanostructures protect the enclosed plasma DNA from degradation by nucleases.	Mao et al. (2001), Cao et al. (2019)
Chitosan bound conjugate	Delivery of encapsulated conjugates	Precisely aim for cells.	Hu et al. (2016); Jing et al. (2019)
Chitosan encapsulated drugs	luorescein drug gets effective delivery, facilitating delivery of curcumin	Effective drug transport to ocular mucosal epithelium, improved therapeutic efficacy of curcumin.	Caprifico et al. (2020), Hu and Luo (2021)

Table 2
Various microbial infections and its implications

Infections	Description	Reference
Bacterial	Bacterial infections can be transmitted through various means, requiring enough organisms to survive in the environment and reach a susceptible host for dissemination. Many bacteria have adapted to endure in water, soil, food, and other settings. Some utilize vectors like animals or insects as intermediaries before infecting another human. The development of bacterial infection and disease is influenced by several factors. Firstly, the infectivity of an organism determines the number of individuals infected relative to those susceptible and exposed. Secondly, pathogenicity gauges the potential of an infectious organism to induce disease, with pathogenic bacteria possessing traits that enable them to elude the body's defences and exploit its resources. Lastly, virulence pertains to an organism's inclination to cause disease, encompassing features such as invasiveness and toxin production. Host factors play a crucial role in determining whether disease ensues following the transmission of a bacterial agent. These factors encompass genetic makeup, nutritional status, age, duration of exposure to the organism, and existing illnesses. The environment also contributes to host susceptibility, with factors like air pollution, chemicals, and environmental contaminants weakening the body's defence against bacterial infections.	Doron and Gorbach (2008)
Viral	Viral infections can instigate widespread diseases in humans, ranging from mild to severe, often carrying the potential for fatality unless effectively managed. Acute viral infections exhibit a sudden and rapid onset of illness, which can either be swiftly resolved by the host's robust innate immune responses or, alternatively, lead to the demise of the host. Following viral infection, components of innate immunity, including physical barriers, diverse phagocytic cells, a group of cytokines, interferons (IFNs), and IFN-stimulated genes, constitute the initial defence line for clearing the virus. Innate immunity not only plays a crucial role in the swift elimination of viruses but can also contribute to disease progression by causing immune-mediated damage to the host's tissues. While elements of the antiviral innate immune response are equipped to counter viral invasion, viruses have evolved various strategies to evade host immune surveillance, ensuring the establishment of successful infections.A comprehensive understanding of the intricate mechanisms governing the interaction between viruses and the host's innate immune system is essential for devising rational treatment strategies for acute viral infectious diseases.	Rai et al. (2021); Tompa et al. (2021)

Continued on next page

Table 2 continued

Fungal	Fungal infections pose a significant public health threat, especially in the context of patients with various diseases, including Covid-19, where they are linked to potentially life-threatening mycoses and increased mortality rates. These infections encompass a spectrum of conditions, ranging from superficial and cutaneous to sub-cutaneous, mucosal, and systemic infections, each varying in severity. Organisms like Candida spp., which are normally part of the human microbiota, can give rise to opportunistic infections in individuals. In immunocompromised patients, such as those with HIV, cancer patients undergoing chemotherapy, and individuals receiving immunosuppressive drugs, these infections can escalate to invasive candidiasis, posing a serious threat. Beyond opportunistic and systemic infections, fungal pathogens such as Candida, Aspergillus, Fusarium, Mucorales, and molds contribute to healthcare-associated infections (HAI) in patients with underlying illnesses. In specific geographical regions, these fungal pathogens are responsible for prevalent and life-threatening endemic mycoses, including Blastomycosis, Coccidioidomycosis, Histoplasmosis, Talaromycosis, Paracoccidioidomycosis, and Sporotrichosis.	Reddy et al. (2022)
Protozoal	Protozoal infections, typically confined to specific regions due to climatic conditions and the presence of intermediate hosts facilitating transmission to humans, are now being observed beyond their original geographical boundaries. This is likely attributed to the rise in international travel and the migration of individuals from their native regions. It is crucial to have a comprehensive understanding of these infectious diseases, especially given the association with immunosuppression, whether it be related to HIV infection, solid organ transplantation, or bone marrow transplant involving prolonged immunosuppressive drug regimens. Such immunosuppression can lead to more severe clinical manifestations and a reduced response to specific treatments. A notable proportion of these cases has been documented in immigrants relocating from tropical countries to non-tropical regions. It is imperative for healthcare professionals dealing with these patients to heighten their awareness of these diseases, as this can contribute to more effective management and prevention strategies.	Chimelli (2011)

2.3.1 *Infections and inflammation*

Microbes typically cause infections, and inflammation is regarded as one of the organism's responses to pathogens. It is a standardized reaction and serves as a mechanism of innate immunity (Hentschel et al., 2021). Table 2 gives a brief description on various types of infection that lead to inflammation.

A substantial body of knowledge has been generated concerning the applications of chitin (CT), a natural biopolymer, and its N-deacetylated form, chitosan (CS), across various fields. Extensive research has been conducted to investigate both the anti-inflammatory and proinflammatory potential of chitosan and its derivatives (Pangestuti & Kim, 2010).

In a study conducted by researchers wherein they encapsulated melatonin within chitosan nanoparticles to enhance its effectiveness by increasing the melatonin release properties. Anionic sodium tripolyphosphate (STPP) was used in the ionic gelation process to create chitosan nanoparticles. Both in-vitro and in-vivo therapeutic benefits were investigated in this study. An in-vivo analysis was carried out in an animal model (specific to mice) with DSS-induced ulcerative colitis, and a model including LPS-stimulated macrophages was used to assess the in-vitro therapeutic efficiency. When compared to plain melatonin, the study's results showed that melatonin-chitosan nanoparticles considerably enhanced the anti-inflammatory capabilities in both in-vitro and in-vivo situations (Soni et al., 2021).

With an aim to improve the anti-inflammatory qualities of atorvastatin (AT), improve its surface features, achieve prolonged release, and guarantee site-specific activity,a research was conducted. In this work, AT was encapsulated into AT-PLGA-CS-NPs (F1), which were chitosan-coated PLGA nanoparticles. Following that, F1 and free Atorvastatin were added to Pluronic 127-hydroxymethylpropyl cellulose thermosensitive gels to create formulations F2 and F3, respectively. F4 was a water-based, basic AT suspension. These four formulations' in-vitro release profiles were investigated in the study. The examination also looked at their capacity to irritate the eyes and how well they worked to lessen the inflammation that Prostaglandin E1 (PGE1) had caused in the rabbits' eyes. The results showed that the AT-PLGA-CS-NP thermosensitive gels (F2) were useful for delivering anti-inflammatory drugs to the eyes (Arafa et al., 2020).

An investigation was carried out on the influence of Chitosan Oligosaccharides (COS) on Lipopolysaccharide (LPS)-stimulated RAW 264.7 cells. The findings revealed that exposure to COS dose-dependently reduced the release of TNF-α and IL-6 induced by LPS into the culture medium. Additionally, a parallel reduction in TNF-α and IL-6 at the mRNA level suggested that COS exposure lowered the transcriptional production of these cytokines. Moreover, COS exposure was shown to reduce nitric oxide (NO) secretion in the medium triggered by LPS. Remarkably, the introduction of external TNF-α into the solution counteracted the reduction in IL-6 and NO levels induced by COS, suggesting that COS's anti-inflammatory impact was affected by the TNF-α pathway. They also explored the safeguarding attributes of COS in a model representing renal oxidative stress induced by glycerol-triggered acute renal failure. This study established that COS holds antioxidative characteristics in the kidneys, alleviates the inflammatory reaction triggered by glycerol, and improves renal function.. Additionally, they employed the carrageenan-induced paw edema technique in their investigation (Yoon et al., 2007).

It has been showcased the anti-inflammatory effects of chitosan oligosaccharides (COS) were not only influenced by the dosage but also by their molecular weight, particularly at higher dosages. To explore the in-vivo anti-inflammatory impact of two different COS mixtures, a study was conducted on balb/c mice and the carrageenan-induced paw edema method was employed. The findings indicate that COS exhibits anti-inflammatory properties that vary with the dosage and, notably, the molecular weight, especially at higher levels. A single dosage of 500 mg/kg body weight might effectively address acute inflammation, but further investigation is necessary to ascertain their effectiveness in cases of prolonged inflammation, as well as to explore the bioavailability of these substances (Fernandes et al., 2010)

The findings of a study on the preventive impact of COS (chitosan oligosaccharides) in LPS-induced sepsis illustrated that COS treatment reduced organ damage and enhanced survival rates in mice given an LPS (lipopolysaccharide) injection. After looking at inflammatory markers such neutrophil infiltration and serum levels of IL-1β and TNF-α, the researchers discovered that COS therapy decreased these cytokines. The redox imbalance brought on by LPS-induced sepsis was also reversed by COS therapy; this condition was marked by elevated levels of malondialdehyde (MDA) and decreased levels of glutathione (GSH) and catalase (CAT). Furthermore, LPS-induced signalling pathways such as p38 mitogen-activated protein kinase and c-Jun NH(2)-terminal kinase (JNK) were blocked by COS treatment (MAPK). These results suggest that the protective effect of COS against LPS challenge in mice might be attributed to its anti-inflammatory and antioxidative properties (Qiao et al., 2011).

An innovative chitosan nanosponge intended to enhance the transdermal delivery of Poloxamer-based drugs was introduced in 2011. Chitosan was chosen because it can loosen the tight junctions in the stratum corneum, which allows drugs to penetrate the skin more easily. The research combined two types of chitosan (with molecular weights of 3 and 10 kDa) with Poloxamer 407 using p-nitrophenyl chloroformate. The blended mixtures of these chitosan with Poloxamer 407 in different ratios followed by a simple nanoprecipitation process transform these blends into flexible and soft nanosponges. The chitosan nanosponges (CNSs) showed stability in biological buffers for up to four weeks and had no harmful effects on human dermal fibrocytes. In Franz-type diffusion cells, the CNSs significantly improved the penetration of drugs through human cadaver skin. The 3 kDa Poloxamer exhibited the most

potential as an effective carrier for enhancing transdermal drug delivery (Lee et al., 2021).

In 2017, a research was conducted to investigate the impact of chitosan-based gel to promote wound healing in donkeys. Chitosan solution was prepared by dissolving 0.1% chitosan (w/v) in a 1.0% acetic acid solution. The researchers then mixed one gram of Carbopol 940 with the chitosan solution to create Chitosan gel, which was stored at -20°C until needed. The specific objective of the study was to assess the effectiveness of 0.1% chitosan gel in promoting the healing of equine skin wounds, comparing it to a 2.5% povidone-iodine treatment (used as the control). The clinical findings indicated that wounds treated with chitosan contracted at a faster rate compared to control wounds, with shoulder wounds showing quicker contraction than forearm wounds. Furthermore, all wounds treated with chitosan fully healed with intact epidermis by the end of the experiment. Based on these results, the study suggests that chitosan gel might be more effective than povidone-iodine in promoting equine skin wounds regeneration (Zaid et al., 2017).

A review focused on the function of chitosan in wound healing emphasized the potential of chitosan as a biomaterial attributed to its anti-inflammatory and antibacterial properties. The review stated that effective wound dressings should be tailored to specific wound types, be cost-effective, and minimize discomfort for patients. This requires modifying their physical characteristics. While there is ample information on chitosan and modified chitosan, there is still much to explore in the context of wound healing. Chitin nanofibers, with their potent biological activity, have been proposed for various biomedical applications. For example, they inhibit NF-κB and MCP-1 activation, exerting anti-inflammatory effects. They also hinder fibrosis in a mouse model of acute ulcerative colitis. These findings suggest that chitin nanofibers could be a novel therapeutic option or functional dietary component for people with inflammatory bowel disease (Gokarneshan, 2017).

In a murine model of acute ulcerative colitis caused by dextran sulphate sodium (DSS), Kazuo Azuma and colleagues evaluated the anti-inflammatory and anti-fibrosis characteristics of α-chitin nanofibrils. According to the study's results, α-chitin nanofibrils decreased the regions in colon tissue that showed positive nuclear factor-B staining (measured at 7.2 $\pm$ 0.5% per field in the α-chitin nanofibrils group against 10.7 $\pm$ 0.9% per field in the control group; $p < 0.05$).Furthermore, α-chitin nanofibrils also inhibited the increased positive areas seen in Masson's trichrome staining in colon tissue (6.8 $\pm$ 0.6% per field in the α-chitin nanofibrils group versus 10.1 $\pm$ 0.7% per field in the control group; $p < 0.05$). In contrast, the α-chitin powder suspension did not exhibit these changes in the DSS-induced acute ulcerative colitis mouse model. The study's ultimate conclusion was that α-chitin nanofibrils possess anti-inflammatory attributes by inhibitng NF-B activation and anti-fibrogenic effects in the DSS-induced acute ulcerative colitis mouse model (Azuma et al., 2012).

Table 3
Studies on use of chitosan as carrier in carcinomas .

Drugs	Application	Observation
Doc-etaxel	Lung cancer	Ameliorated immunosuppressive micro environment to promote anti tumor effects
Mitocin C	Hepatocellu-lar carcinoma	High drug concentration at target site and highly effective in supressing tumor growth
Gemc-itabine	Breast Cancer	Minimised side effects and improved therapeutic efficacy
Cisplatin	Ovarian cancer	Controlled drug effect
Methotrex-ate	Cervical cancer	Targeted tumour extracellular drug release
Norcan-tharidin	Hepatocellu-lar carcinoma	Prolonged circulation in blood and reduced distribution to other tissues
Doxoru-bicin	Breast cancer	Site specific breast tumor micro environment drug release
5-Flurouracil	Breast cancer	Controlled drug release
Ara C cytara-bine	Leukemia	pH dependent drug release in an acidic tumor environment
Camp-tothecin	Ovarian cancer	Maximal cancer suppressing effect

Another study in 2017 explored chitosan-based scaffolds for bone regeneration, focusing on their osteoinductive and anti-inflammatory properties. The research involved assessing the ability of these scaffolds to reduce inflammation in human mesenchymal stem cells (hMSCs) triggered by lipopolysaccharide (LPS). Specific interleukins and oxidative stress byproducts (IL-1β, IL-10, and nitrites) related to the immune response were measured. Additionally, the scaffolds were tested in an in-vitro co-culture model mimicking inflammation in osteoporotic sites, involving osteoblasts and LPS-stimulated macrophages. The findings revealed that these bioactivated scaffolds can: i) suppress the production of inflammatory substances like IL-1β; ii) decrease oxidative stress byproducts; and iii) enhance the production of anti-inflammatory markers (IL-10) in hMSCs. Importantly, these bioactivated scaffolds also demonstrated anti-inflammatory effects in in-vitro co-culture systems resembling the compromised bone environment in-vivo (Fasolino et al., 2019).

To evaluate chitosan's effectiveness as a pharmacological agent for treating inflammatory bowel diseases (IBD) with a focus on its anti-inflammatory properties, a study was implemented. The study assessed the effects of 5-aminosalicylic acid (5-ASA) and the molecular weight (MW) and degree of deacetylation (DD) of chitosan in murine experimental colitis. Over the course of three days, chitosan grades with varying MW and DD were administered via rectal route to mice suffering from colitis, either alone or in combination with 5-ASA. Myeloperoxidase (MPO), alkaline phosphatase (ALP), tumour necrosis factor (TNF), interleukin-6 (IL-6), interleukin-1 (IL-1), and nuclear factor kappa-B (NF-κB) levels in the colon were then evaluated by the researchers. The study findings indicate

that colitis-affected mice treated with 30 mg/kg of chitosan alone and 30 mg/kg of 5-ASA for three days showed a substantial decrease in MPO, ALP, TNF, IL-6, IL-1, and NF-κB levels in comparison to untreated mice. Crucially, the anti-inflammatory characteristics of chitosan were not significantly affected by its unique properties, such as DD and MW. The study suggests that chitosan can be utilized together with NSAIDs to enhance its anti-inflammatory activity, particularly when combined with 5-ASA (Jhundoo et al., 2020).

A research focused on investigating the impact of chitosan-alginate nanoparticles (NPs) on inflammatory cytokines and chemokines produced by P. acnes was carried out where human monocytes were activated with P. acnes and subjected to different concentrations of chitosan-alginate NPs after being extracted from peripheral blood. The study revealed that chitosan-alginate NPs effectively suppressed the formation of the inflammatory cytokine IL-12p40, which has a significant impact in the acne-related inflammatory response, in a dose-dependent manner. At the maximum concentration of chitosan-alginate NPs tested, there was nearly complete inhibition of IL-12 protein. Similarly, when human keratinocyte HaCaT cells were exposed to P. acnes in the presence of different concentrations of chitosan-alginate NPs, the study demonstrated that even at low doses, the NPs significantly prevented the initiation of IL-6 by P. acnes in keratinocytes. Importantly, chitosan-alginate NPs showed no harmful effects on human monocytes, unlike the toxic impact of the positive control, sodium chromate, on human monocytes. Moreover, the mild toxicity of NPs on HaCaT cells at higher concentrations was minimal compared to typical amounts of benzoyl peroxide (BP) used in preclinical settings. These results imply that cytokine generation produced by P. acnes in human monocytes and keratinocytes may be inhibited by chitosan-alginate nanoparticles without cytokine release as a result of cell death (Friedman et al., 2013).

To explore the anti-inflammatory, wound healing, and anti-ulcerogenic properties of chitosan, an in-vivo investigation was carried out. The experiment was conducted in Wistar rats and Swiss adult mice. Three types of chitosan were utilized in the research: low molecular weight (107 kDa, 75-85% DD), high molecular weight (624 kDa, 75% DD), and a commercial chitosan (300-350 kDa, 76% DD). In this study, Swiss adult mice (Mus musculus) with body weights ranging from 30 to 40 g were randomly assigned to six groups, each consisting of eight animals, for the investigation. The experiment involved giving different types of chitosan (low molecular weight, high molecular weight, and commercial) to groups III to V at different concentrations (0.5% for low molecular weight and commercial, and 1% for high molecular weight). The chitosan was dissolved in acetone. Acetone was introduced to Group I as negative control. Dexamethasone at a concentration of 4 mg/mL, along with chitosan was introduced to Group II as the positive control. Croton oil, a proinflammatory agent, at a concentration of 5% in acetone was given to Group IV. Apart from group VI, where HMW chitosan was applied at 1% in acetone, croton oil (5% in acetone) was administered to the inner surface of the right ear for each group after a 60-minute interval. Simultaneously, all animals received 20 μl of acetone on the inner surface of their left ear. After 4 hours, the animals were humanely euthanized by cervical dislocation, and standard sections measuring 6 mm in diameter were excised from both ears and weighed individually. Croton oil-induced edema was determined as the weight difference (right ear - left ear) for each animal, expressed in percentage, with the results presented as the average for each group. The research revealed that high molecular weight (HMW) chitosan played a role in preserving the stomach lining, providing gastroprotective benefits, while low molecular weight (LMW) chitosan notably reduced ethanol-induced ulcerative ulcers. These results suggest that chitosan could have practical applications in peptic ulcer management. Furthermore, HMW chitosan promoted healing in both normal and diabetic rats by stimulating collagen synthesis, possibly without triggering fibroblast growth (Tavaria et al., 2016).

2.4. Chitosan in carcinomas

Chitosan being a biocompatible, biodegradable natural polysaccharide, and its non-immunogenic and nontoxic nature has potential in treating various types of tumours. Table 3 quotes few examples explored by researchers in the same direction (Ding & Guo, 2022).

3. CONCLUSION

This review has highlighted the promising role of chitosan as an anti-inflammatory agent. Chitosan, a natural biopolymer derived from chitin, exhibits a broad range of anti-inflammatory properties. It has been shown to mitigate inflammation through various mechanisms, such as modulating cytokine expression, scavenging free radicals, and regulating immune responses. The versatility of chitosan, its biocompatibility, and minimal side effects make it a valuable candidate for the development of anti-inflammatory therapies. Nevertheless, further research is required to perfectly comprehend its precise mechanisms of action and optimize its applications. As our understanding of chitosan's anti-inflammatory potential deepens, it opens doors to innovative approaches for managing inflammatory conditions, providing hope for enhanced treatments and a better quality of life for individuals suffering from such ailments.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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