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Chitosan clinical application: a literature review

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### **Abstract**

**Background:** Chitosan, a natural polysaccharide derived from chitin, has emerged as a versatile biomaterial with significant clinical applications due to its biocompatibility, biodegradability, and inherent bioactivity. This literature review explores the multifaceted roles of chitosan across three key domains: wound healing, cosmetic science and drug delivery systems.

**Objective:** This literature review explores the current evidence surrounding the therapeutic use of Chitosa, drawing on preclinical animal studies, systematic reviews, and clinical trials, classified using the Oxford Centre for Evidence-Based Medicine (OCEBM) Levels of Evidence.

**Method:** A comprehensive search of electronic databases was conducted to identify relevant studies on the use of Chitosan. Studies were included if they reported on the use of Chitosan clinically, animal study related to Chitosan.

**Results:** This review highlights chitosan's immense potential across wound healing, drug delivery systems, and cosmetic applications. In wound healing, chitosan accelerates tissue repair through its biocompatibility, antimicrobial activity, and hemostatic properties, as supported by various preclinical studies. In cosmetics, its film-forming ability and moisturizing properties enhance skin hydration, anti-aging effects, and hair care formulations. Drug delivery systems leverage chitosan's mucoadhesive nature, enabling controlled and targeted release of therapeutics. However, challenges such as variability in properties and regulatory hurdles remain critical barriers to clinical adoption.

**Conclusion:** Chitosan is a versatile biomaterial with significant potential in healthcare and cosmetic science. While preclinical evidence underscores its efficacy in wound healing, drug delivery, and skin and hair care, challenges in standardization, scalability, and regulatory compliance persist. Addressing these limitations through rigorous clinical trials and regulatory frameworks is essential to fully harness chitosan's transformative capabilities for clinical and commercial success.

Keywords: chitosan, wound healing, drug delivery, cosmetics, biopolymers, nanoparticles, hydrogels, clinical applications.

## **Introduction**

Chitosan, a biopolymer derived from the deacetylation of chitin, has garnered significant attention in the medical and pharmaceutical fields due to its unique physicochemical properties and remarkable versatility [1]. As a naturally occurring polysaccharide, chitosan is biocompatible, biodegradable, non-toxic, and inherently bioactive, making it an ideal candidate for a wide range of biomedical applications [2]. Its cationic nature, rare among natural polymers, allows it to interact with negatively charged biological membranes, enhancing its functionality in various therapeutic and cosmetic contexts [3]. Over the years, extensive research has been conducted to explore the potential of chitosan in wound healing, drug delivery systems, and cosmetic science, leading to innovative solutions for some of the most pressing challenges in healthcare and personal care [5].

One of the most promising applications of chitosan is in wound healing, where its biocompatibility, antimicrobial activity, and ability to promote hemostasis make it an effective material for managing both acute and chronic wounds. Chitosan-based products, including hydrogels, sponges, membranes, and nanofibers, have been shown to accelerate tissue repair by stimulating fibroblast proliferation, angiogenesis, and collagen deposition [6]. These properties, combined with its capacity to provide a moist healing environment and reduce infection risks, have positioned chitosan as a valuable material in the development of advanced wound care products [7].

Chitosan has also emerged as a multifunctional ingredient in cosmetic science, where its film-forming ability, antimicrobial activity, and capacity to retain moisture are leveraged to enhance skin hydration, promote wound repair, and improve hair strength and texture [8]. Recent advancements in chitosan hybrids and chemically modified derivatives have further expanded its applications in anti-aging, acne management, and hair care products [9].

In drug delivery, chitosan's mucoadhesive properties and ability to transiently open epithelial tight junctions enable enhanced drug absorption across mucosal surfaces [10]. Its versatility in forming nanoparticles, microspheres, and hydrogels allows for the encapsulation and controlled release of a wide range of therapeutic agents, including hydrophobic drugs, proteins, and nucleic acids [11]. These features make it particularly suitable for targeted drug delivery in cancer therapy, vaccine delivery, and gene therapy, offering improved efficacy and reduced side effects [12].

This review aims to provide a comprehensive overview of the clinical and preclinical evidence supporting chitosan’s applications in wound healing, drug delivery, and cosmetics. While the potential of chitosan is significant, challenges such as variability in its physicochemical properties, scalability, and regulatory hurdles must be addressed to fully realize its clinical and commercial potential.

## Materials and methods

Keywords including “Chitosan”, “Chitin”, “Clinical Applications”, “Clinical Use”, “Therapeutic usage”, “Therapy”, were searched in the MEDLINE, PubMed and Ovid databases for relevant studies published on clinical trials, diagnosis and treatment. Some papers were further reviewed using a double-blinding approach, sample size, control usage, randomization usage and objective endpoint measurements. All studies were classified according to the Oxford Center for evidence-based medicine evidence hierarchy (Fig.1) [13].

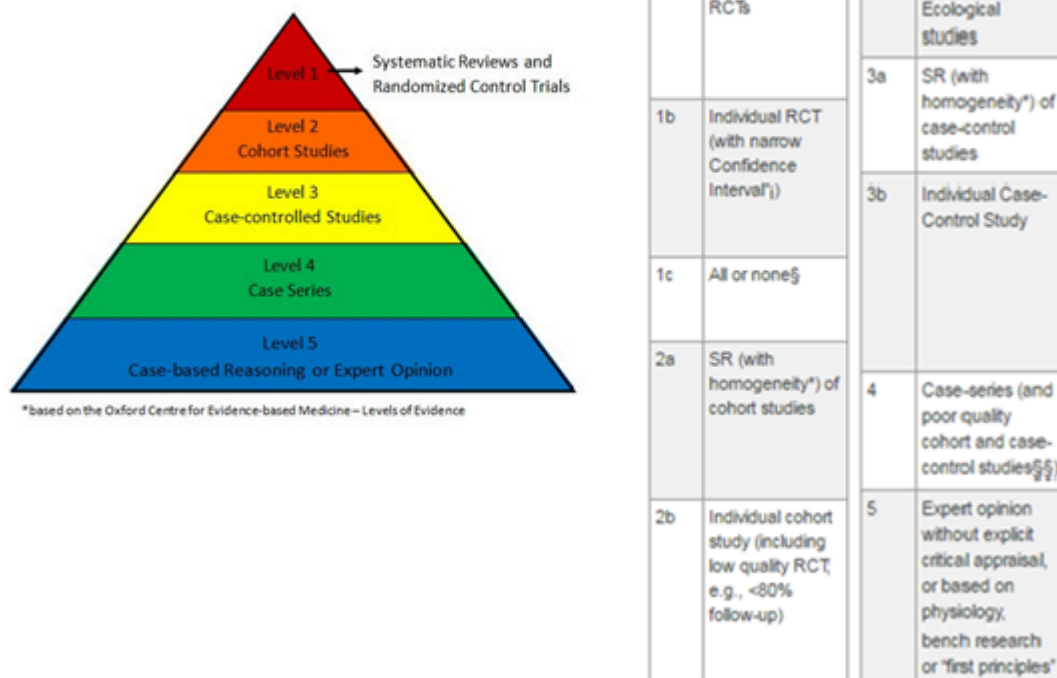


Fig. 1 Evidence Hierarchy according to Oxford Centre for Evidence-Based

Medicine [13]. RCT, randomized controlled trials; SR, systematic review.

## **Result**

### **Wound healing**

Patrulea et al. [14] provides a comprehensive review of chitosan's clinical applications, particularly focusing on its potential in wound healing. The authors explore the functionalization of chitosan with bioactive molecules, such as growth factors and peptides, to further improve its therapeutic efficacy.

The review also examines various chitosan-based wound dressing formulations, including hydrogels, sponges, and nanofibers, which offer controlled drug release and moisture retention for optimal wound healing environments. Clinical studies are summarized, demonstrating chitosan's effectiveness in treating burns, diabetic ulcers, and surgical wounds. However, challenges such as variability in chitosan's physicochemical properties and regulatory barriers are acknowledged, necessitating further standardization and research (Level V).

Ueno and colleagues [15] explores the potential of chitosan for topical formulations and its applications in wound healing. The authors emphasize its hemostatic ability, which aids in controlling bleeding, and its role in accelerating wound healing by stimulating fibroblast proliferation, collagen synthesis, and angiogenesis.

The review details various chitosan-based topical formulations, such as gels, films, and sponges, and their applications in wound treatment. These formulations offer advantages such as moisture retention, controlled drug delivery, and protection against microbial infections. Preclinical and clinical studies are reviewed, demonstrating chitosan's effectiveness in treating burns, skin ulcers, and surgical wounds. The article also discusses the chemical modifications of chitosan, such as carboxymethylation and quaternization, to enhance its solubility and bioactivity, thereby expanding its utility in wound care (Level V).

Dai and coworkers [16] reviews the antimicrobial and wound-healing effects of chitosan preparations, focusing on their use in managing wounds and burns. The authors emphasize chitosan's ability to inhibit bacterial and fungal growth, which is critical for preventing infections in wounds and burns. Chitosan's positive charge allows it to interact with negatively charged microbial cell membranes, disrupting their integrity and leading to cell death.

The review also highlights chitosan's role in wound healing by promoting hemostasis, enhancing fibroblast activity, and stimulating the deposition of extracellular matrix components such as collagen. These properties are particularly valuable for accelerating tissue repair and regeneration. The authors discuss various forms of chitosan preparations, such as films, sponges, hydrogels, and nanoparticles, and their applications in wound care (Level V). regulatory approval of chitosan-based wound care products.

Ahmed et al. [17] review the applications of chitosan-based scaffolds in wound healing, emphasizing their versatility and effectiveness as biomaterials. The antimicrobial activity of chitosan is discussed, with a focus on its interaction with microbial cell membranes, which helps reduce infection risks in wounds. Functionalization of chitosan scaffolds with bioactive agents like growth factors, drugs, and nanoparticles is reviewed as a strategy to enhance their therapeutic potential.

The review summarizes preclinical and clinical evidence demonstrating the efficacy of chitosan-based scaffolds in treating a variety of wounds, including diabetic ulcers and burns. However, the authors acknowledge limitations such as variability in the molecular structure of chitosan and the need for further research to optimize scaffold design and ensure regulatory compliance (Level V).

Liu and colleagues [7] investigate the development and application of a functional chitosan-based hydrogel as a wound dressing and drug delivery system, highlighting its potential for enhancing wound healing. The study emphasizes the hydrogel's dual functionality: first, as a wound dressing that protects against infection and maintains an optimal healing environment, and second, as a drug delivery system that enables the sustained release of therapeutic agents, such as antibiotics and growth factors. Preclinical experiments using animal models demonstrate the hydrogel's ability to enhance wound closure rates, reduce inflammation, and promote angiogenesis and collagen deposition.

While the study showcases promising results, challenges such as scalability, cost, and variability in chitosan's properties are noted, along with the need for further clinical trials to confirm efficacy and safety in humans (Level IIIb).

Azad et al. (2004) explore the use of chitosan membranes as wound-healing dressings, providing insights into their characterization and clinical application. The study focuses on the structural and functional properties of chitosan membranes, such as their ability to maintain a moist environment, promote cell adhesion, and accelerate tissue regeneration. Results demonstrated that

the membranes effectively reduced healing time, controlled infection, and minimized scar formation. The study also highlights the ease of application and removal of the membranes, which improves patient comfort.

While the findings underline the potential of chitosan membranes in wound management, challenges such as variability in chitosan's molecular weight and deacetylation degree are discussed, along with the need for further optimization and regulatory validation (Level IIb).

Moeini and colleagues [19] provide a detailed review of chitosan-based wound dressings and their incorporation of active secondary metabolites to enhance wound healing and antimicrobial effects. The review focuses on the synergistic effects achieved by integrating secondary metabolites, such as polyphenols, essential oils, and flavonoids, into chitosan-based wound dressings. These metabolites enhance the antimicrobial efficacy of chitosan and contribute to anti-inflammatory, antioxidant, and tissue-regenerative properties.

The authors discuss the molecular mechanisms by which chitosan-based dressings promote wound healing, including enhanced fibroblast proliferation, angiogenesis, and collagen synthesis. The ability of these dressings to create a moist environment, reduce infection risks, and support sustained drug release is emphasized. Preclinical studies demonstrate notable improvements in wound healing outcomes using these composite dressings, providing evidence for their potential clinical applications. However, challenges such as variability in chitosan properties, limited standardization, and the need for extensive clinical trials are acknowledged (Level V).

Liu and coworkers [21] present a systematic review on the role of chitosan in wound healing, consolidating evidence from preclinical and clinical studies. This review systematically examines the molecular and biological mechanisms by which chitosan facilitates wound healing, including its ability to promote fibroblast proliferation, angiogenesis, and collagen synthesis.

The review evaluates various chitosan-based formulations, such as hydrogels, membranes, and sponges, emphasizing their capacity to provide a moist wound environment, support sustained drug release, and enhance tissue regeneration. Clinical studies included in the review demonstrate that chitosan significantly enhances healing outcomes in chronic and acute wounds, such as diabetic ulcers and surgical incisions. However, the authors note limitations in the current evidence, including small sample sizes and heterogeneity in study designs. Standardization of chitosan formulations and further large-scale clinical trials are recommended to confirm and optimize its efficacy (Level IIa).

Miguel et al. [21] provide a comprehensive review of chitosan-based asymmetric membranes and their applications in wound healing. The authors highlight the advantages of using chitosan in these membranes, including its biocompatibility, biodegradability, antimicrobial activity, and ability to promote hemostasis and tissue regeneration.

The review emphasizes how the unique structure of asymmetric membranes supports the wound-healing process by maintaining a moist environment, reducing infection risks, and enabling sustained drug delivery. Preclinical studies reviewed demonstrate that chitosan-based asymmetric membranes significantly improve healing outcomes, particularly in chronic wounds such as diabetic ulcers (Level V).

Kojima and colleagues [22] investigate the effects of chitin and chitosan on collagen synthesis during wound healing, focusing on their biological role in tissue repair. The study evaluates the impact of chitin and chitosan on fibroblast activity and collagen production in a rat wound model. Results demonstrate that both chitin and chitosan significantly enhance fibroblast proliferation and collagen deposition, with chitosan showing a stronger effect due to its superior biocompatibility and bioactivity.

The authors propose that chitosan's positive charge enables interactions with negatively charged cell membranes, stimulating cellular responses that promote wound healing. Additionally, chitosan exhibits antimicrobial activity, which reduces infection risks and creates an optimal healing environment. The study concludes that chitin and chitosan are effective in accelerating wound healing, particularly through their influence on collagen synthesis (Level IIIb).

Che and coworkers [23] provide a comprehensive review of the applications of chitosan-based hydrogels in wound healing. The review explores how chitosan-based hydrogels create an optimal environment for wound healing by maintaining moisture, reducing infection risks, and supporting cellular activities such as proliferation and migration.

The authors discuss the molecular mechanisms by which chitosan-based hydrogels promote wound healing, including the stimulation of fibroblast activity, angiogenesis, and collagen synthesis. Additionally, they emphasize the versatility of hydrogels as platforms for delivering therapeutic agents, such as antibiotics, growth factors, and nanoparticles, directly to the wound site. The review also highlights the challenges of clinical translation, including variability in chitosan properties, scalability, and regulatory hurdles (Level V).

Loo et al. [24] review the application of chitosan-based nanoparticles (CSNPs) in promoting skin wound healing, emphasizing their potential as advanced

biomaterials for wound care. The authors discuss how CSNPs contribute to wound healing through multiple mechanisms, including promoting fibroblast proliferation, stimulating angiogenesis, and enhancing collagen deposition. CSNPs are particularly effective as carriers for bioactive compounds, such as growth factors, antibiotics, and anti-inflammatory agents, enabling controlled and sustained drug release at the wound site.

The review also addresses the challenges of using CSNPs in clinical applications, including scalability, variability in nanoparticle synthesis, and regulatory hurdles. The authors advocate for more clinical trials to validate the safety and efficacy of CSNPs in human wound care (Level V).

Okamoto and colleagues [25] evaluate the effects of chitin and chitosan on open wound healing in dogs, investigating their potential as wound-healing agents in veterinary medicine. The experimental study involved applying chitin and chitosan to open wounds in dogs, with wound area reduction and histological changes monitored over time. Results demonstrate that chitosan significantly accelerates wound closure compared to control groups, primarily due to its ability to promote granulation tissue formation and enhance collagen synthesis.

The study concludes that chitosan, in particular, holds promise as an effective wound-healing agent in veterinary applications, though further research is needed to evaluate its efficacy in other species and to optimize its formulations (Level IIIb).

Cui and coworkers [26] explore the application of electrospun chitosan nanofibers in wound healing, emphasizing their potential to enhance tissue regeneration and repair. The study discusses the advantages of chitosan nanofibers, including their ability to maintain a moist environment, control infection, and deliver bioactive agents such as antibiotics and growth factors. Preclinical studies highlighted in the review demonstrate that electrospun chitosan nanofibers significantly accelerate wound closure, reduce inflammation, and promote angiogenesis and collagen deposition.

The authors identify challenges such as scalability, mechanical strength of the nanofibers, and variability in chitosan properties. They call for further optimization and clinical trials to validate the safety and efficacy of electrospun chitosan nanofibers in human wound care (Level V).

Burkatovskaya et al. [27] investigate the effects of a chitosan acetate bandage on the healing of infected and noninfected wounds in a mouse model. The study evaluates the bandage's ability to accelerate wound closure, reduce bacterial load, and promote tissue regeneration in wounds deliberately infected with *Pseudomonas aeruginosa* and in noninfected wounds.

Results show that the chitosan acetate bandage significantly accelerates wound healing in both infected and noninfected wounds compared to untreated controls. In infected wounds, the bandage reduces bacterial counts, likely due to chitosan's intrinsic antimicrobial properties, which inhibit bacterial growth.

The study concludes that chitosan acetate bandages are effective in improving wound healing outcomes, particularly in infected wounds, and could have potential applications in both clinical and emergency settings (Level IIIb).

Zhang and colleagues [28] present a study on chitosan-based self-healing hydrogels as advanced wound dressings. The authors emphasize the hydrogel's ability to maintain a moist environment, reduce infection risks, and provide sustained delivery of therapeutic agents, such as antibiotics, growth factors, and anti-inflammatory drugs. The self-healing capability of the hydrogel is achieved through reversible cross-linking, allowing the material to adapt to mechanical stress and extend its durability over the wound site.

The hydrogel's self-healing property ensures that it adheres well to irregular wound surfaces and remains effective over time, minimizing the need for frequent dressing changes. The study concludes that chitosan-based self-healing hydrogels have significant potential for clinical applications, although challenges such as large-scale production and regulatory approval remain (Level V).

Wang and coworkers [29] evaluate the potential of chitosan-alginate polyelectrolyte complex (PEC) membranes as wound dressings, specifically assessing their impact on incisional wound healing in a rat model. Chitosan is combined with alginate, another biocompatible and biodegradable polysaccharide, to form a PEC membrane with improved mechanical strength and wound-healing properties. The results demonstrate that the chitosan-alginate PEC membrane significantly enhances wound healing compared to untreated wounds. The membrane provides a moist environment conducive to healing, reduces scar formation, and exhibits mild antimicrobial activity, which helps minimize infection risk.

The authors conclude that the chitosan-alginate PEC membrane is a promising material for wound dressings due to its biocompatibility, mechanical durability, and ability to promote tissue regeneration (Level IIIb).

Wang et al. (2021) explore the clinical potential of chitosan in wound healing, focusing on its procoagulant and antimicrobial properties. The study highlights chitosan's positive charge, which interacts with negatively charged cell membranes to promote blood clotting and disrupt bacterial membranes, reducing the risk of infections. The authors emphasize that chitosan-based

wound dressings, such as hydrogels, films, and powders, provide a moist healing environment while simultaneously enhancing fibroblast proliferation, angiogenesis, and collagen synthesis.

While preclinical results are promising, the clinical application of chitosan-based materials requires further validation through large-scale human trials. The study concludes that chitosan holds significant potential as a multifunctional wound healing material, but scalability, regulatory approval, and formulation optimization remain key challenges (Level IIIb).

### **Skin and hair care**

Guzmán and colleagues [31] provide a comprehensive review of chitosan's applications as a multifunctional cosmetic ingredient in skin and hair care. The study focuses on chitosan's ability to enhance skin hydration, provide antimicrobial protection, and improve the structural integrity of hair.

For skin care, chitosan forms a protective barrier that retains moisture, making it effective for hydrating dry or damaged skin. Its film-forming properties also help protect the skin from environmental stressors and pollutants. In hair care, chitosan improves hair texture and strength by forming a thin film around hair strands, reducing breakage and enhancing shine. It also has conditioning properties and can be used in shampoos, conditioners, and styling products.

The review highlights the versatility of chitosan in cosmetic formulations and its potential for further functional enhancements through chemical modifications (Level V).

Rejinold and coworkers [9] review the advancements in chitosan-based hybrid materials for cosmeceutical applications, focusing on their use in skin, hair, and dental care. The review highlights the development of hybrid chitosan formulations, where chitosan is combined with other materials, such as nanoparticles, peptides, or bioactive compounds, to enhance its effectiveness in cosmeceuticals.

The review underscores the potential of chitosan hybrids to deliver active ingredients more effectively, thanks to their improved stability and controlled release properties. Despite their promise, the authors call for more clinical trials to validate their safety and efficacy in real-world applications (Level V).

Aranaz et al [32] review the applications of chitin, chitosan, and their derivatives in cosmetics and cosmeceuticals, focusing on their utility in skin and hair care. Chitosan forms a film on the skin, enhancing hydration by preventing water loss and offering a protective barrier against environmental

damage. For hair care, chitosan derivatives improve hair texture by forming a thin film around hair strands, enhancing shine and reducing brittleness.

The review highlights the potential of chemically modified chitosan to enhance its functionality, such as improving solubility and targeted delivery of active ingredients. While preclinical and in vitro studies are promising, the review emphasizes the need for clinical trials to validate chitosan's efficacy in real-world cosmetic applications (Level V).

Kulka and colleagues [8] provide a comprehensive review of chitosan-based materials and their applications in the cosmetic industry, with a focus on their use in skin and hair care products. Chitosan demonstrates excellent moisturizing and anti-aging properties. Its ability to form a protective film on the skin helps retain moisture and shield the skin from external pollutants and irritants in skin care. Chitosan-based formulations improve hair strength, texture, and shine for hair care. It is commonly used in shampoos, conditioners, and styling products for its ability to enhance manageability and reduce frizz.

The review highlights the potential for chemically modified chitosan to expand its applications and improve its performance. However, the authors emphasize the need for clinical studies to validate the real-world efficacy of chitosan-based cosmetics (Level V).

Thambiliyagodage and coworkers [4] provide an extensive review of recent advancements in chitosan-based applications in skin and hair care. The review highlights chitosan's wide-ranging applications in skin and hair care products due to its unique ability to enhance hydration, support tissue regeneration, and protect against environmental damage.

The review emphasizes the potential for chitosan-based materials to be chemically modified to enhance their solubility, bioactivity, and targeted delivery capabilities. However, the authors stress the importance of clinical trials to validate its real-world effectiveness in cosmetic applications (Level V).

Hirano et al. [33] explore the early applications of chitin and chitosan in cosmetics and pharmaceuticals, focusing on their role in skin and hair care. The study highlights their ability to enhance hydration, protect against environmental damage, and promote tissue regeneration. In skin care, chitosan forms a film on the skin, providing a moisturizing effect by reducing transepidermal water loss. In hair care, chitosan improves the texture and strength of hair by forming a protective coating around hair strands. This coating reduces brittleness, enhances shine, and protects hair from damage caused by heat and chemicals. Chitosan is used in shampoos, conditioners,

and styling products for its ability to enhance hair manageability and reduce frizz.

The authors emphasize the versatility of chitosan in cosmetic and pharmaceutical applications. However, the study notes the need for further research to optimize formulations and expand its applications (Level V).

Lee and colleagues [34] report the development of a novel chitosan-based nanocapsule designed to enhance skin penetration and deliver cyclosporin A (CsA) for improved therapeutic effects in skin and hair care. The study highlights the nanocapsule's biocompatibility, stability, and ability to overcome the limitations of conventional CsA formulations, such as poor water solubility and limited skin absorption. The nanocapsule provides controlled and sustained release, resulting in prolonged therapeutic effects while minimizing systemic side effects in skin care. The study also demonstrates that CsA-loaded chitosan nanocapsules significantly promote hair regrowth *in vivo*.

The authors conclude that chitosan nanocapsules offer a promising platform for delivering bioactive compounds like CsA in skin and hair care, enabling targeted and effective treatments (Level IIIb).

Kim and coworkers [35] present a study on poly( $\gamma$ -glutamic acid)/chitosan hydrogel nanoparticles designed for the effective delivery of fermented herbal extracts (FHE) to promote hair growth. The study focuses on the nanoparticles' ability to preserve the bioactivity of FHE while enhancing its delivery to hair follicles, thereby improving therapeutic efficacy. The hydrogel nanoparticles combine chitosan and poly( $\gamma$ -glutamic acid), taking advantage of chitosan's biocompatibility, biodegradability, and antimicrobial properties. The nanoparticles protect the active ingredients in FHE from degradation and facilitate their controlled release. This ensures sustained bioavailability at the target site.

The authors conclude that poly( $\gamma$ -glutamic acid)/chitosan hydrogel nanoparticles are a promising platform for delivering bioactive ingredients to enhance hair growth. This approach addresses challenges in preserving the stability and bioactivity of natural extracts while ensuring efficient delivery to hair follicles (Level IIIb).

Lee et al. [36] examines the multifunctional properties of chitosan in cosmetic applications, emphasizing its roles in skin and hair care. The study notes that chitosan promotes wound healing and supports collagen synthesis, making it effective for anti-aging and skin repair products. In hair care, chitosan improves hair manageability, strength, and shine. It provides a protective coating around hair strands, reducing breakage and minimizing damage from

heat and chemical treatments. Its conditioning properties make it suitable for shampoos, conditioners, and styling products.

The study concludes that chitosan is a versatile and multifunctional ingredient in cosmetics, with potential for further applications. However, the research emphasizes the need for more clinical studies to optimize its formulations and validate its efficacy in real-world use (Level V).

Naeini and colleagues [37] investigate the use of chitosan and its amphiphilic derivative nanoparticles as carriers for Minoxidil to enhance hair growth. The study aims to address challenges in Minoxidil delivery, such as limited penetration into hair follicles and systemic side effects, by utilizing chitosan-based nanoparticles for targeted and controlled release.

In vitro studies demonstrated that these nanoparticles provided sustained release of Minoxidil over time, maintaining its therapeutic concentration. In vivo experiments on animal models showed significant hair growth induction in terms of increased hair density, follicle size, and thickness compared to conventional Minoxidil formulations. The nanoparticles enabled deeper penetration into the scalp, targeting hair follicles more effectively while reducing systemic absorption and associated adverse effects (Level IIIb).

Ferreira and coworkers [38] review the recent developments in the use of chitosans and nanochitosans for skin protection, regeneration, and repair, emphasizing their potential in cosmetic and therapeutic applications. In skin care, chitosans and nanochitosans form a protective film on the skin, reducing transepidermal water loss and maintaining hydration. These materials exhibit excellent antimicrobial activity, making them effective for managing acne and preventing skin infections. Nanochitosans are particularly valuable for their enhanced penetration into the deeper layers of the skin, enabling the delivery of bioactive compounds, such as antioxidants and anti-inflammatory agents.

The review also discusses advances in modifying chitosans to improve their solubility, stability, and bioactivity. The authors note that the nanoscale formulation of chitosan enhances its efficacy and expands its potential applications in skin protection and repair (Level V).

Casadidio et al. [39] provide a detailed review of the properties, eco-friendly production processes, and cosmetic applications of chitin and chitosan. The study emphasizes their biocompatibility, biodegradability, and multifunctional properties, which make them ideal for use in skin and hair care products.

The review highlights the eco-friendly production of chitosan from marine waste, aligning with sustainability trends in cosmetics. The authors

underscore the need for further research to optimize formulations and validate the efficacy of chitosan in real-world applications (Level V).

Xia and colleagues [40] investigate the development of collagen-chitosan scaffolds incorporating insulin-like growth factor 1 (IGF-1) and bone marrow-derived mesenchymal stem cells (BM-MSCs) for promoting wound healing and hair follicle regeneration. The study highlights the synergistic effects of these components in enhancing skin repair and stimulating hair growth. The collagen-chitosan scaffolds provide a biocompatible and biodegradable matrix that supports cell adhesion, proliferation, and migration.

In vivo experiments demonstrated that the scaffolds significantly improved wound healing rates, increased dermal thickness, and facilitated the regeneration of new hair follicles. The study also reported reduced inflammation and enhanced angiogenesis, critical for wound repair and hair follicle health. The authors conclude that IGF-1 and BM-MSC-incorporating collagen-chitosan scaffolds are a promising platform for advanced wound care and hair regrowth therapies. The combination of bioactive molecules, stem cells, and chitosan-based scaffolds represents a synergistic approach to skin and hair regeneration (Level IIIb).

### **Drug delivery systems**

Bernkop-Schnürch and coworkers [41] examine the clinical potential of chitosan-based drug delivery systems, highlighting their advantages in improving drug efficacy, stability, and bioavailability. The review emphasizes chitosan's role in oral drug delivery, where its mucoadhesive nature prolongs the retention time of drugs at the absorption site, enhancing bioavailability.

In targeted drug delivery, chitosan nanoparticles and hydrogels can encapsulate drugs, protecting them from degradation and enabling controlled and sustained release. These systems are particularly effective in delivering drugs to mucosal tissues, such as the gastrointestinal, nasal, and pulmonary systems. Additionally, chitosan derivatives have been developed to improve solubility and functionality, expanding its application to a wide range of drugs, including poorly water-soluble compounds. The authors conclude that chitosan-based systems hold significant promise in clinical drug delivery but stress the importance of conducting further clinical trials to optimize formulations and validate their safety (Level V).

Naskar et al. [42] review two decades of research on chitosan-based nanoparticles as drug delivery systems. The review emphasizes the use of chitosan nanoparticles in targeted and controlled drug delivery. These

nanoparticles protect encapsulated drugs from enzymatic degradation, improve solubility, and allow sustained release, reducing dosing frequency. Their ability to interact with negatively charged mucosal surfaces enhances residence time at the site of absorption, improving bioavailability. This makes them particularly effective for delivering drugs to the gastrointestinal tract, nasal cavity, and pulmonary system.

The review also discusses the incorporation of hydrophobic drugs, peptides, and nucleic acids into chitosan-based systems, expanding their scope in drug delivery. The authors conclude that while preclinical studies demonstrate promising results, large-scale clinical trials are essential to establish the safety and efficacy of chitosan-based nanoparticles in human applications (Level V).

Mitra and colleagues [43] explore the use of chitosan microspheres in novel drug delivery systems, focusing on their benefits in improving drug efficacy, bioavailability, and targeted delivery. The review highlights the advantages of chitosan microspheres, such as their ability to encapsulate both hydrophilic and hydrophobic drugs, protect drugs from degradation, and enable sustained release over extended periods. Chitosan's mucoadhesive properties enhance drug retention at the site of delivery, while its cationic nature allows interaction with negatively charged biological membranes, promoting drug absorption.

Chitosan microspheres have been explored for pulmonary, nasal, and ocular drug delivery, offering localized and targeted drug administration. Chemical modifications, such as grafting functional groups or introducing cross-linking agents, further optimize the properties of chitosan microspheres for specific applications. The authors conclude that chitosan microspheres hold significant promise in drug delivery, but further clinical trials are necessary to validate their safety, efficacy, and scalability for therapeutic use (Level V).

Abd Elgadir and coworkers [44] review the role of chitosan composites and chitosan nanoparticle composites in enhancing various drug delivery systems. The review focuses on the integration of chitosan with other biopolymers and its nanoscale derivatives to improve drug stability, bioavailability, and controlled release. Chitosan composites are highlighted for their ability to encapsulate drugs, protect them from degradation, and provide sustained drug release, reducing dosing frequency.

The review also emphasizes the chemical modifications of chitosan composites, such as grafting functional groups or blending with other polymers, to improve solubility, mechanical strength, and drug-loading capacity. These advancements expand the utility of chitosan in delivering hydrophobic drugs, peptides, and nucleic acids. The authors conclude that chitosan composites and nanoparticles have significant potential for clinical

drug delivery, but further studies, particularly clinical trials, are needed to validate their effectiveness (Level V).

Nagpal et al. [45] review the potential of chitosan nanoparticles as a versatile system for novel drug delivery. The review discusses the advantages of chitosan nanoparticles in improving drug bioavailability, protecting drugs from enzymatic degradation, and enabling controlled and sustained release. Such properties are particularly beneficial for the delivery of peptides, proteins, and nucleic acids, which are typically challenging to administer due to poor stability and permeability.

The authors emphasize the role of chitosan nanoparticles in targeted drug delivery, where functionalization with ligands enables site-specific drug release, such as in cancer therapy or gene delivery. Additionally, the review explores chemical modifications to chitosan, such as grafting hydrophilic or hydrophobic groups, to further improve solubility, stability, and drug-loading capacity (Level V).

Haider and colleagues [46] provide a comprehensive review of recent advancements in chitosan-based drug delivery systems. The review discusses the use of chitosan nanoparticles, hydrogels, microspheres, and films in targeted and controlled drug delivery. Functionalization strategies, such as grafting ligands or polymers, have enabled the development of highly specific drug delivery systems for applications in cancer therapy, gene delivery, and treatment of chronic diseases.

Chitosan's mucoadhesive properties are highlighted as crucial for oral, nasal, and pulmonary delivery, enhancing drug absorption and bioavailability. The authors conclude that chitosan-based drug delivery systems hold immense promise for therapeutic applications. However, they emphasize the need for further clinical research to optimize formulations, address scalability challenges, and validate efficacy in human applications (Level V).

Casettari and coworkers [47] review the use of chitosan-based nasal delivery systems for therapeutic drugs in their article. It emphasizes the advantages of nasal delivery, including its non-invasive nature, rapid onset of drug action, and potential for systemic delivery by bypassing hepatic first-pass metabolism.

The review also explores chitosan derivatives, such as trimethylated and thiolated chitosan, which further enhance mucoadhesion, solubility, and permeability. Chitosan-based nasal systems have been investigated for a range of therapeutic applications, including insulin delivery, hormone therapy, and vaccines. The authors conclude that chitosan-based nasal delivery systems show great promise for therapeutic drug delivery, but additional

clinical trials are needed to confirm their safety, efficacy, and scalability (Level V).

De Campos et al. [48] investigate the potential of chitosan nanoparticles as innovative systems for ocular drug delivery. The research covers the in vitro stability and in vivo behavior of chitosan nanoparticles, demonstrating their ability to protect encapsulated drugs and sustain their release. The study also evaluates the cellular toxicity of chitosan nanoparticles, finding that they exhibit low toxicity to ocular tissues, making them safe for use in drug delivery. These nanoparticles are explored for various therapeutic applications, including treatments for glaucoma, infections, and inflammatory eye diseases (Level IIIb).

Illum and colleagues [49] review the use of chitosan as a novel nasal delivery system for vaccines, focusing on its ability to enhance mucosal immunity and improve vaccine delivery. The review highlights the advantages of nasal delivery systems for vaccines, including their non-invasive nature, ease of administration, and ability to elicit both systemic and mucosal immune responses.

The study discusses preclinical and experimental evidence showing that chitosan-based nasal vaccine formulations induce robust immune responses. Applications include vaccines for influenza, diphtheria, tetanus, and other infectious diseases. The authors conclude that chitosan-based nasal vaccine delivery systems hold significant promise, but further clinical trials are required to validate their safety, immunogenicity, and scalability (Level V).

## **Discussion**

Chitosan, a biopolymer derived from chitin, has demonstrated its versatility as a biomaterial with significant potential for clinical applications. This discussion synthesizes findings from the literature, exploring chitosan's applications in wound healing, drug delivery, and cosmetics, while highlighting its strengths, limitations, and future research directions.

## **Wound Healing**

Chitosan's role in wound healing is underpinned by its biocompatibility, antimicrobial properties, and ability to promote tissue regeneration. Studies by Patrulea et al. [14] and Ueno et al. [15] emphasize its hemostatic effects and capacity to enhance fibroblast proliferation, angiogenesis, and collagen deposition, which are critical components of the healing cascade. Chitosan-based wound dressings, including hydrogels, sponges, membranes, and nanofibers, have been shown to accelerate healing in burns, diabetic ulcers, and surgical wounds. For example, Liu et al. [7] highlighted the dual

functionality of chitosan hydrogels as both wound dressings and drug delivery systems, enabling sustained release of therapeutic agents.

Despite these advantages, challenges remain, particularly in the variability of chitosan's molecular weight and degree of deacetylation, which can impact its performance. Moeini et al. [19] and Miguel et al. [21] underscore the need for standardization and regulatory compliance to ensure consistency in clinical outcomes. Additionally, while preclinical studies demonstrate promising results, clinical trials are limited, and large-scale studies are needed to validate efficacy in diverse patient populations.

### **Cosmetic Applications**

Chitosan's film-forming ability, antimicrobial activity, and capacity to retain moisture have positioned it as a multifunctional ingredient in cosmetic science. Guzmán et al. [31] and Aranaz et al. [32] highlight its applications in skin hydration, anti-aging formulations, and acne management. Chitosan's ability to form a semi-occlusive film on the skin reduces transepidermal water loss, while its antimicrobial properties prevent infections in acne-prone skin.

In hair care, chitosan improves texture, strength, and shine by forming a protective coating around hair strands. Studies by Lee et al. [34] and Kim et al. [35] reveal the potential of chitosan-based nanoparticles and hydrogels to enhance the delivery of bioactive compounds, such as Minoxidil and fermented herbal extracts, thereby promoting hair growth and reducing hair loss.

Despite these advancements, the real-world efficacy of chitosan in cosmetic products remains underexplored. Most studies reviewed, such as those by Kulka et al. [8] and Rejinold et al. [9] are preclinical or in vitro, with limited clinical validation. Future research should prioritize large-scale clinical trials to substantiate these findings and address consumer safety concerns.

### **Drug Delivery**

Chitosan has emerged as a promising platform for drug delivery due to its mucoadhesive properties, biodegradability, and ability to transiently open epithelial tight junctions. This allows for enhanced drug absorption and targeted delivery. Nagpal et al. [45] and Haider et al. [46] highlight the versatility of chitosan in forming nanoparticles, hydrogels, and microspheres, enabling controlled and sustained release of drugs. Applications include oral, nasal, ocular, and transdermal drug delivery, with particular success in cancer therapy, vaccine delivery, and gene therapy.

Notably, Casettari et al. [47] explored chitosan's potential in nasal drug delivery systems, emphasizing its ability to bypass first-pass metabolism and

deliver macromolecules such as peptides and proteins. Similarly, De Campos et al. [48] demonstrated the efficacy of chitosan nanoparticles in ocular drug delivery, where drug retention and absorption are often challenging.

However, scalability and safety remain critical barriers to clinical adoption. Abd Elgadir et al. [44] emphasize the need for further studies to optimize formulations and address regulatory hurdles. While preclinical research is robust, clinical trials are essential to confirm safety and efficacy, particularly in chronic conditions and high-risk populations.

### **Strengths and Limitations**

One of chitosan's greatest strengths lies in its versatility. Its intrinsic properties like biocompatibility, biodegradability, and bioactivity allow it to be tailored for diverse applications. Functionalization with bioactive molecules, such as growth factors, peptides, and nanoparticles, further enhances its therapeutic potential. Additionally, chitosan's antimicrobial activity provides a dual advantage in both wound healing and cosmetics, reducing infection risks while promoting tissue repair or enhancing skin health.

However, chitosan's clinical adoption faces several limitations. Variability in its physicochemical properties, such as molecular weight and degree of deacetylation, poses challenges in standardization and reproducibility. Regulatory hurdles, particularly in drug delivery and cosmetics, further complicate its translation from the laboratory to clinical practice. Moreover, while preclinical studies are abundant, the lack of large-scale, high-quality clinical trials limits the strength of evidence, as most studies fall under Level 5 in the Oxford Centre for Evidence-Based Medicine hierarchy.

### **Future Directions**

To fully realize chitosan's potential, several areas warrant further exploration:

1. **Standardization:** Efforts should focus on standardizing chitosan's manufacturing processes to ensure consistency in its molecular properties. This is critical for regulatory approval and reproducibility across studies.
2. **Clinical Trials:** Large-scale, randomized controlled trials are essential to validate the efficacy and safety of chitosan-based formulations in wound healing, drug delivery, and cosmetics.
3. **Combination Therapies:** The integration of chitosan with other biomaterials or bioactive agents offers opportunities for synergistic effects. For instance, combining chitosan with stem cells or growth factors could enhance tissue regeneration and wound healing.

4. Regulatory Framework: Collaborative efforts between researchers, industry stakeholders, and regulatory bodies are needed to streamline the approval process for chitosan-based products.
5. Consumer Acceptance: In cosmetics, consumer acceptance is critical. Studies should address potential allergenicity and long-term safety to build consumer trust.

## Conclusion

Chitosan represents a transformative biomaterial with promising applications in wound healing, drug delivery, and cosmetics. While preclinical evidence highlights its efficacy, significant gaps in clinical validation, standardization, and regulatory compliance must be addressed. By addressing these challenges, chitosan can transition from an experimental biomaterial to a mainstream solution in clinical and commercial settings, delivering significant benefits to patients and consumers alike.

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