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CHITOSAN: A MULTIFUNCTIONAL BIOPOLYMER FOR ENHANCED WOUND HEALING WITH ANTIMICROBIAL, HAEMOSTATIC, AND ANALGESIC PROPERTIES, SUPPORTED BY CLINICAL EVIDENCE

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Wound healing is a complex physiological process that repairs tissue integrity with stages including hemostasis, inflammation, proliferation, and remodeling. The primary aim of wound management is to avert infection, limit necrotic tissue development, expedite the healing process, and reduce scar formation. Chitosan (CS) is a biopolymer that has been extensively studied for its potential use in wound healing applications. This is due to its biocompatibility, biodegradability, non-toxicity, antimicrobial, haemostatic, and analgesic properties. Protection against bacteria, algae, and fungi is the source of its antimicrobial properties. Chemical modifications have improved the haemostatic activity and analgesic properties of the CS, which enhance patient comfort during the recovery phase. Furthermore, CS and its derivative have attracted much attention due to the accelerated wound healing. This review examines the synthesis, structural characteristics, and inherent properties of CS, as well as its potential applications in wound treatment, with a focus on antimicrobial efficacy, haemostatic capabilities, analgesic effects, and relevant clinical studies.

Keywords*: Chitosan, Antimicrobial, Wound healing, Hemostatic, Analgesic, Clinical studies*

INTRODUCTION

Wounds are any injury that disrupts the normal structure of the skin and physiological functions. The cause of this wound may be genetic disorders, acute trauma, injury, or surgical interventions[1]. They are generally classified as open or closed, depending on their type. Furthermore, wounds may be categorized as either acute or chronic [2]. Acute wounds can be caused by several factors, including radiation, extreme temperature changes, or chemical exposure. It takes 8–12 weeks for this type of wound to heal naturally. Chronic wounds, on the other hand, require a lengthy healing period, which can last several months due to persistent inflammation[3]. Wounds are classified based on their etiology, type, depth, and clinical appearance[4], as displayed in **Fig. 1.**

Wound healing is a complicated process that describes the interaction of various components, including immune cells (such as macrophages, monocytes, neutrophils, and lymphocytes) and non-immune cells (such as keratinocytes, endothelial cells, and fibroblasts), extracellular matrix (ECM) components, and soluble mediators (such as growth factors and cytokines)[5]. The healing rate of acute wounds differs from that of chronic wounds and is influenced by the immune system. Wound healing usually happens in four stages: hemostasis, inflammation, proliferation, and remodeling[6] **(Fig. 2)**. The first stage of the process is recognized as hemostasis, during which a newly produced fibrin clot provides a protective barrier against external elements, allowing for optimal moisture retention [7]**.** After

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hemostasis, the inflammatory stage begins, in which damaged tissues produce pro-inflammatory cytokines. This attracts circulating white blood cells, and degranulated platelets and activated macrophages respond by releasing a variety of growth factors[8]. The subsequent proliferation phase is characterized by critical processes, including angiogenesis, epithelialization, the formation of granulation tissue, the manufacture of ECM components, and wound contraction[9]. The collagen molecules are self-assembled into a distinctive triple helical structure and subsequently released into the extracellular space as this phase moves forward. Here, they establish stable cross-links that provide strength and stability to the tissue. In comparison to dermal collagen, which is typically distinguished by its strength and organization, the collagen structures in scar tissue are smaller and weaker. Please be aware that the characteristics of uninjured skin are never entirely reestablished in injured tissue[10]. The last stage is remodeling, which is defined as the transformation of granulation tissue into scar tissue over a six- to twelve-month period[11]. Scars, including hypertrophic scars like keloids, can develop as a result of excessive granulation tissue formation and an abundance of collagen [11]. Innovative methods are required for managing bacteria-infected wounds. In this case, the use of biocompatible and absorbable polymers, including CS[12], hyaluronic acid [13], and polycaprolactone [14]. CS has been recognized as a desirable material for wound healing. This is attributed to its specific set of biological properties, which include biocompatibility, biodegradability, and low toxicity [15]. It can also accelerate wound healing and has antibacterial, mucoadhesive, and hemostatic properties[16]. This review discusses the synthesis, structures, properties, and applications of CS as a starting material for antimicrobial, hemostatic, analgesic, and wound healing purposes.

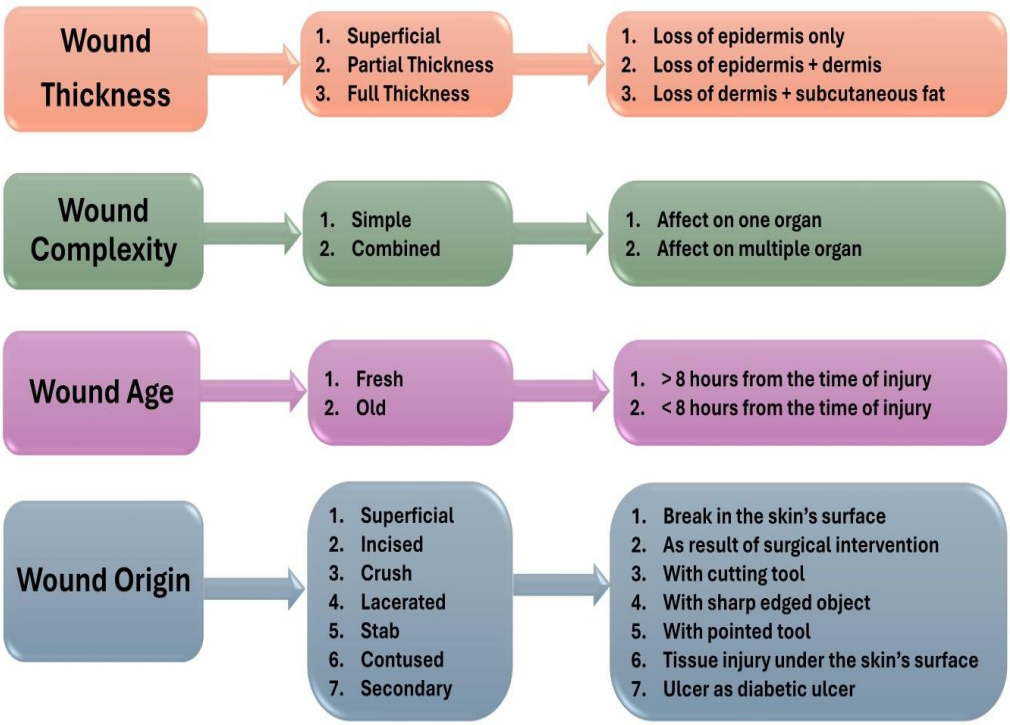

Fig. 1: Wound classification with respect to thickness, complexity, age and origin [4].

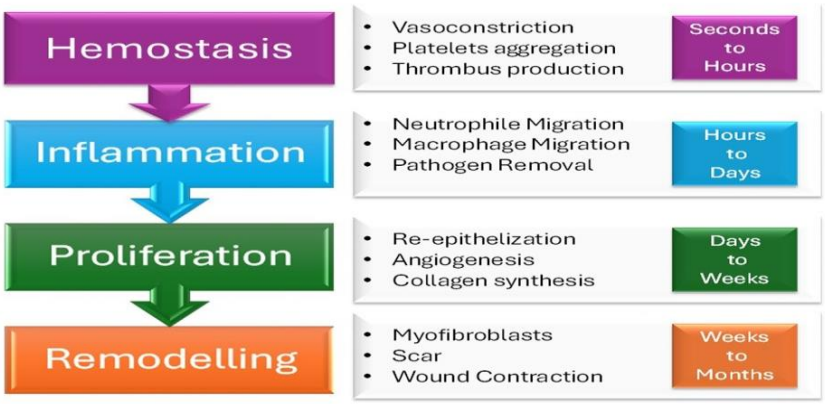

Fig. 2: Wound healing phases [17].

Chitosan

Synthesis, structures, and properties

CS is a biological polymer obtained from chitin. It is a desirable substance for a variety of applications in biomedical sciences, agriculture, and environmental research as it is biodegradable, biocompatible, and safe for human health [18].

Synthesis of Chitosan

Chitin is used as the raw material for CS. Chitin is primarily derived from crustacean shells, especially crab and shrimp shells. The purifying procedure is easier for thinner shrimp shells [19]. The processes used to produce CS from shells are shown in **(Fig. 3)**. Because of their structural diversity, different chitin sources require different treatments. Therefore, there is no universal purification method. Typically, the process is divided into demineralization (elimination of calcium carbonate), deproteinization (elimination of proteins), and decolorization phases, which can be performed by chemical method or biological method [20]. Final products must be extensively purified, especially if they are employed in pharmaceutical applications, since residual minerals, proteins, or colors might have major adverse consequences. CS can be produced from chitin by either enzymatic or chemical deacetylation[21,22]. Chemical deacetylation is more frequently employed in commercial preparation due to its cost-effectiveness and the feasibility of mass manufacturing[23]**.** Chitin may be converted to CS by either enzymatic or chemical deacetylation:

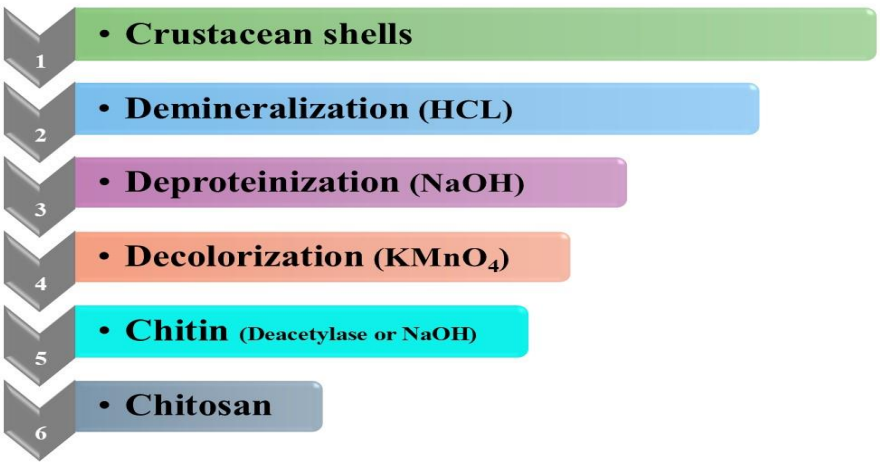

Fig. 3: The processes of chitosan production from shells [24].

Chemical Deacetylation

Chemically, alkaline and acidic substances can be employed to deacetylate chitin. However, because glycosidic linkages are more sensitive to acid, alkali deacetylation is more commonly performed[22,25]. Chitin N-deacetylation can be conducted homogeneously[26] or heterogeneously[27]. The homogeneous approach produces alkali chitin via dispersing chitin in concentrated sodium hydroxide (30 g NaOH/45 g H2O/ 3 g Chitin) for 3 hours or longer at 25 °C, then dissolving in grinding ice at 0 °C. This approach produces a CS with good solubility and an average acetylation level of 48%-55%[26]. On the other hand, the heterogeneous method, Chitin undergoes treatment using a hot concentrated solution of sodium hydroxide for a few hours, leaving CS as an insoluble residual deacetylated to around 85%-99%. In addition, alterations in CS production may result in changes in the arrangement of acetyl groups throughout the chains, viscosity, and molecular weight in solution[22]**.** Deacetylation by chemical method has some limitations including waste of energy and concentrated alkaline solution, resulting in increased environmental contamination, and a wide and diverse spectrum of soluble and insoluble compounds

Enzymatic Deacetylation

A new biological method utilizing chitin deacetylases has been investigated to circumvent these restrictions in CS manufacturing. The use of this enzyme for the conversion of chitin to CS provides the prospect of a regulated, non-degradable development, leading to the synthesis of unique, well-distinct CS [28]. This approach is specifically designed to produce CS oligomers. Chitin deacetylase enhances the hydrolysis of N-acetamido linkages in chitin, producing CS. These deacetylation activities have been observed in numerous insect and fungus species [22,25].

Structure of Chitosan

CS consists of D-glucosamine and N-acetyl-D-glucosamine units linked by β-(1–4) glycosidic linkage [29]**.** The structure can be represented as: $(C_6H_{11}NO)_n$ D-Glucosamine + $(C_6H_{11}NO_4)_m$ N-Acetyl-D-Glucosamine [30]**.** These units are attached through β-(1→4) glycosidic bonds, making a copolymer with a random distribution of GlcN and GlcNAc along the polymer chain **(Fig. 4).** The proportion of these units is determined by the deacetylation degree, which plays a crucial role in defining the properties and functionality of CS [24]**.**

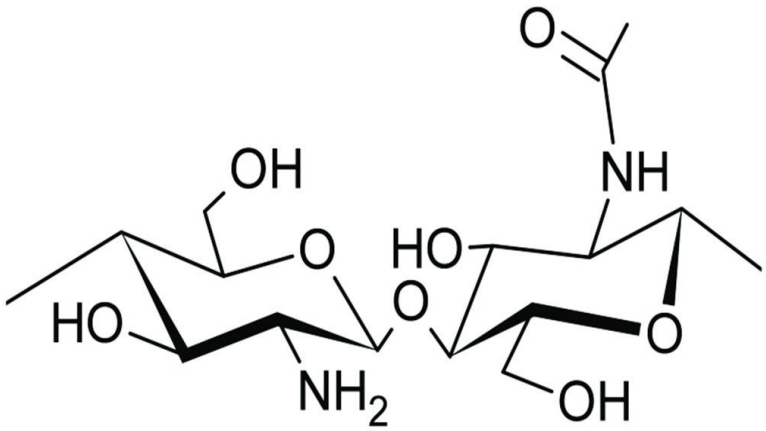

Fig. 4: Chemical structure of chitosan [31].

Chitosan Physicochemical Properties

CS is a natural biodegradable polymer with several beneficial properties. It has many intrinsic properties, such as biocompatibility, biodegradability, cationic nature, and nontoxicity. These properties make CS a versatile material. Most of the properties of CS emerge from their physicochemical features, including molecular weight, deacetylation degree, solubility and viscosity:

Molecular weight

Molecular weight (M.wt) has a considerable influence on the physicochemical and biological properties of CS. The molecular weight of CS depends on its source material and how it gets produced and extracted [32]. Based on molecular weight, CS can be grouped into low molecular weight (LMWT) (<100 kDa), medium molecular weight (MMWT) (100–1000 kDa), and high molecular weight (HMWT) (>1000 kDa) [33]. LMWT of CS is preferred for use in biological and commercial applications since it is more stable and solubilized [34]**.**

Deacetylation degree

The deacetylation degree is another aspect that influences CS's activity, physicochemical characteristics, and use. The rate of deacetylation is the arrangement of amino groups along the polymer chain [24]**.** The cationic behaviour of CS in acidic conditions is due to the amino group in its polymeric chain. Thus, the deacetylation degree has a significant role in viscosity and solubility [35]. Whether the polymer is chitin or CS can be identified from the degree of deacetylation. When the degree of deacetylation exceeds 50%, that commonly indicates the effective conversion of chitin into CS [36]**.**

Solubility

CS has good solubility in acidic solvents but has bad solubility in alkaline or neutral solvents. However, chitin is typically insoluble in most solvents; deacetylating yields soluble CS with primary amino groups and a pKa of 6.5[30]. When CS is dissolved in acidic solutions, the amine becomes positively charged due to protonation, leading to an increased solubility of CS. However, as the pH reaches 6 or above, they become insoluble due to losing their charge[24,25]. Polymer crystallinity, pH, temperature, molecular weight, and deacetylation degree can affect CS's solubility[24]**.**

Viscosity

The degree of deacetylation and the molecular weight of CS significantly influence viscosity, one of the parameters affecting its industrial application. CS becomes more viscous as the deacetylation degree rises and the molecular weight falls [34]. It can also rely on the particle size and storage duration of CS. At the same concentration, nano CS has a viscosity 30% lower than that of regular CS. Nano CS noted a 17% decrease in viscosity after 24 hrs of storage, compared to regular CS's 10% decline [37]**.**

Potential features of chitosan for wound treatment

Antimicrobial properties

The most recent article discusses the antimicrobial properties of CS, which are determined by its physical characteristics**.** **Table (1)** summarizes the applications of CS in antimicrobial effects. CS has been highly evaluated in both in vivo and in vitro studies as an antimicrobial agent against various organisms, including bacteria, fungi, and algae[38]. In these investigations, CS is typically categorized as either bactericidal, indicating its ability to kill bacteria, or bacteriostatic, referring to its capacity to inhibit bacterial growth without necessarily causing bacterial death [39]**.** CS's binding to microbial DNA is another proposed mechanism that inhibits mRNA and protein synthesis by allowing it to enter the nuclei of microorganisms [40]**.** In this case, it is predicted that CS molecules may penetrate through the bacterial cell wall, which is made up of multiple layers of cross-linked murein and reach the plasma membrane. Confocal laser scanning microscopy revealed the presence of CS oligomers (chains with a small number of monomer units) in E. coli treated with CS under various conditions [41]. Raafat *et al.* indicated that, despite being recognized as a possible mechanism, the rate of its occurrence is relatively low [42]**.** A comparative study of the influence of CS on Escherichia coli (Gram-negative) and Staphylococcus aureus (Gram-positive)

bacteria revealed that the mechanisms of CS's antimicrobial activity differed between the two groups of bacteria. The antimicrobial activity of Gram-positive Staphylococcus aureus increased as the molecular weight of CS increased. Furthermore, the antimicrobial activity of Gram-negative Escherichia coli increased as their molecular weight decreased [43]. The most preferred model involves the interaction between positively charged CS molecules and negatively charged microbial cell membranes. The electrostatic forces between the protonated NH^{+3} groups and the negative residues in this model are believed to be responsible for mediating the interaction [44], as they compete with Ca^{+2} for electronegative sites on the membrane surface [42]. This electrostatic interaction induces a dual mode of interference: (i) it alters the permeability of the microbial membrane, leading to internal osmotic imbalances that inhibit microbial growth; and (ii) it promotes the hydrolysis of peptidoglycans in the cell wall, causing leakage of intracellular components, such as potassium ions and other low molecular weight compounds, including proteins, glucose, and lactate dehydrogenase [45]. This investigation [46] employed three sources of CS: Blaps lethifera (CSB), Pimelia fernandezlopezi (CSP), and Musca domestica. Musca domestica had the highest CS yield on a dry basis, at 57.9%. Blaps Lethifera and Pimelia Fernandezlopezi yielded 50.0% and 41.6%, respectively. CS from CSB, CSP, and CSM had deacetylation (DD) rates of 87.1%, 88.2%, and 84.1%, respectively. According to X-ray powder diffraction (XRD), CS isolated from Blaps Lethifera had the highest crystallinity. CS extracts showed strong antibacterial activity against a wide range of bacteria, including gram-positive and gram-negative strains like Bacillus subtilis, Staphylococcus aureus, Listeria innocua, and Pseudomonas aeruginosa. In another study, Li *et al*. investigated the antibacterial activity of non-crosslinked CS scaffolds against common oral pathogens such as Gram-negative Porphyromonas gingivalis and Gram-positive Streptococcus mutans. At 6 h, 1 mg CS scaffolds effectively killed both pathogens through time-dependent bacteria clustering [47]. In this investigation, Mahaninia *et al*., discovered that Schiff's base reaction could be employed to generate multifunctional CS-based hydrogels by establishing reversible imine linkages within CS and a novel vanillin-based cross-linker at room temperature [48]. The approach of functionalizing vanillin with phosphorus compounds to produce an organic flame-retardant cross-linker with high aromaticity was highly promising due to its enhancement of both flame-retardancy and antibacterial properties.

Table 1: Studies of chitosan antimicrobial effect.

Polymer	**Dosage form**	**References**
Chitosan	Film	39
Chitosan	Hydrogels	40
N, O-carboxymethylated chitosan	Solution	41
Low-molecular-weight chitosan	Solution	42
Chitosan	Solution	43
Chitosan	Solution	44
Low molecular weight chitosan	Solution	42
Chitosan	Hhydrogel	45
Chitosan	Solution	46
Chitosan	Scaffold	47
Chitosan	Hhydrogel	48
Low molecular weight chitosan	Nanofibrous dressing	50
Chitosan	Solution	51
Chitosan/sodium tripolyphosphate (TPP)	Nanoparticles	52
Chitosan	Gel	53

In another study, Asvar *et al*. conducted a study aimed at developing wound dressings with enhanced antimicrobial efficacy, particularly against multi-drug resistant (MDR) strains. MDR is a kind of acquired resistance of microorganisms and cancer cells to chemotherapic drugs that are characterized by different chemical structures and different mechanisms of action. It is the consequence of the overexpression of a variety of proteins that extrude the chemotherapic from the cell, lowering its concentration below the effective one [49]. The study sought to incorporate three antimicrobial nanoparticles into a CS-based nanofibrous mat and evaluate its antimicrobial activity against MDR bacteria [50]**.** In addition, Sousa *et al***.** suggested that the antibacterial activity of CS could be improved by modifying it with phthalic anhydride (QF) and subsequently reacting it with ethylenediamine (QFE)[51]. Additional research Amini *et al*. recommends that antibiotic-loaded CS/sodium tripolyphosphate (TPP) nanoparticles be further developed and examined to enhance their antibacterial efficacy against Acinetobacter baumannii, as well as to evaluate their safety and practicality in vivo [52].

Clinical studies

In clinical studies, CS is employed to have an antimicrobial effect. The clinical efficacy of CS in the therapy of chronic periodontitis (CP) as both an active agent and a gel-based carrier was reported by Akncbay *et al*. [53]. A total of 15 patients with moderate-to-severe CP were chosen for this consideration. In CP patients, CS gel (1% w/w) was prepared and administered as an adjunctive treatment to scaling and root planning rather than the control group. The CS gel was incorporated with or without 15% metronidazole. Clinical parameters improved significantly in all groups from baseline to week 24. Patients did not experience any complications associated with the CS for the duration of the study. Because of its antimicrobial properties, the authors proposed that CS used alone or in combination with metronidazole, is effective in the treatment of CP.

Hemostatic properties

Hemostasis is the process of preventing bleeding and keeping blood within a damaged blood vessel. This is the first phase of wound management [54]. Ancient people used herbs, greasy substances, and animal hides mediated by sand for hemostatic treatment[55]. As biotechnology has advanced, a variety of hemostatic agents derived from natural polymers have emerged. So, dressings made of CS biopolymer are thought to be the most applicable way to prevent bleeding [56]. CS-derived hemostatic agents are currently applied to patients to manage post-extraction bleeding [57]. Haemostatic materials are classified into three categories: polysaccharides, inorganic minerals, and proteins. Protein-type hemostatic materials include thrombin, fibrinogen, collagen, and fibrin. Conversely, inorganic minerals include zeolite, kaolin, bentonite, and porous silica. Cellulose, starch, and CS are examples of polysaccharide-based haemostats[58]. Each type of hemostatic material has its unique properties, features, and applications. Because of its antifungal, antibacterial, and non-toxic properties, it is increasingly being used as a biocompatible and biodegradable biopolymer approved for use as wound dressings by the US Food and Drug Administration (FDA)[59].

The hemostatic effect of CS was investigated by numerous researchers. The hemostatic capability of CS was reported to be enhanced by carboxymethylation and crosslinking modifications when combined with carrageenan[60]**.** Blood clotting is synergistically influenced by the porosity of CS nanofibers and gelatin [61]. Yang *et al*. compared solid CS and its solution in acetic acid. It was discovered that solid-state CS and CS-acetic acid physiological saline solution had different hemostatic mechanisms. When blood was mixed with a CS-acetic acid physiological saline solution, the erythrocytes aggregated and deformed [62]. Nonetheless, CS in a solid form with a high level of deacetylation binds more platelets and has a stronger hemostatic effect [63]**.** In another study, Gheorghiță *et al*. analyzed CS-based hemostatic biomaterials and discussed recent advances in their performance, mechanism of action, efficacy, cost, and safety[16]**.** In an *in vivo* model, Pogorielov *et al*. aimed to evaluate the interaction of human blood cells with a variety of CS-based materials of varying molecular weight and CS concentration, as well as to demonstrate their

efficacy[63]. Singh *et al*. also intended to compare the efficacy, cytocompatibility, and biocompatibility of the developed dressing with the marketed formulation (Axiostat®) of a dual functionalized CS-based biodegradable, bio-adhesive fast-acting hemostatic dressing. [64]. In their investigation, Tripathi *et al*. evaluated the efficacy of collagen and CS-based dressings in terms of wound healing and hemostatic effects. The blood interaction affinity was established in vitro using Surface Plasmon Resonance (SPR), and the effectiveness of the developed biopolymer-coated gauze was assessed on Sprague-Dawley rats using gamma scintigraphy[65].

In another study, Bano *et al*. examined the potential of CS and its derivatives as wound dressings and offered a concise understanding of the properties of CS that are necessary for skin healing and regeneration. They placed a particular emphasis on the emerging role of CS films as next-generation skin substitutes for the treatment of full-thickness wounds[55]. Zielińska *et al*. proposed a risk-management-based research program to develop two types of topical hemostatic agents: CS/alginate lyophilized foam and CS/alginate impregnated gauze [66]. Furthermore, Merchan *et al*. were to explain the role of fibrin glue and CS-based dressings (CBDs) in hemophilia patients. Local fibrin glue and CBDs are not always required to achieve hemostasis during all surgical procedures performed on hemophiliacs [67]. In their study, Kang *et al*. targeted creating and evaluating CS dressings treated with sodium hydroxide (NaOH) and/or sodium tripolyphosphate (Na5P3O10) for hemostatic applications[68]. To evaluate the safety of CM and maize starch, Kang *et al*. were required to investigate the mechanical properties, water swelling, and morphology of the two materials using varying ratios of a glyoxal crosslinking agent. Utilizing the blood clotting index, the hemostatic property of the CM/starch foam was evaluated to ascertain its feasibility as a disposable, low-cost haemostatic material. Additionally, the foam's cytotoxicity was assessed through the MTT assay [69]. Additionally, Kadyseva *et al*. conducted a study to identify physicochemical characteristics that will enable the prediction of hemostatic activity in CS and LHA during the raw material selection and LHA creation processes[70].

In another study, Nepal *et al*. evaluated the synthesis, characteristics, and properties of hemostatic sponges. It included a variety of materials, including CS, alginate, hyaluronic acid, cellulose, starch, polyethylene glycol, synthetic polymers, silver nanoparticles, mesoporous silica nanoparticles, and zinc oxide nanoparticles [71]. Another study, Huang *et al*. aimed to investigate the properties of the HM-CHI biopolymer's ability to act as a rapid blood clotting agent. They investigated the synthesis and structural properties of HM-CHI -blood substances using X-ray diffraction, infrared spectroscopy, and elemental analysis [72]. In their study, Zhang *et al*. aimed to prepare a series of AC/GO composite sponges (ACGS), study their mechanical strength and biocompatibility, evaluate the hemostatic efficacies by in vitro whole blood clotting time (WBCT), thromboelastography (TEG), and an in vivo rabbit femoral injury model, and clarify the haemostatic mechanism by studying erythrocyte and platelet adhesion and aggregation using SEM[73]. In another investigation, Santos *et al*. conducted an experimental study to assess the hemostatic effects of two organic substances, a CS membrane and a collagen sponge coated with thrombin and human fibrinogen (TachoSil®), in sealing 7-0 needle stitch holes on rats' femoral arteries, as well as local histological reactions[74].

Clinical studies

The hemostatic effect of CS was investigated in clinical studies. In the initial study, Sarkar *et al*. compared the impact of platelet-rich fibrin (PRF) and CS hydrogel on socket healing in patients undergoing dental extractions while receiving antiplatelet therapy. The study focused on evaluating the hemostatic properties and healing outcomes associated with these materials. Sixty patients on oral antiplatelet therapy were randomly assigned to two groups: 30 received PRF, and 30 were treated with CS hydrogel. Key parameters, including bleeding time, secondary pain, postoperative bleeding, scarring, soft-tissue dehiscence, and alveolar osteitis, were assessed. The findings revealed that the CS hydrogel group demonstrated a shorter

bleeding time, highlighting superior hemostatic effects, whereas the PRF group reported reduced postoperative pain, reflecting enhanced patient comfort[57]**.** The effects of CS on hemostasis in patients with oral anticoagulant therapy were discovered in Kumar's study. Thirty patients, aged 18 to 90, were enrolled, with individuals having seafood allergies excluded from participation. The study employed a split-mouth design and included patients on oral anticoagulant therapy with an international normalized ratio (INR) of ≤ 4, without altering their therapy during the surgical procedure. The results showed that coagulation at the control sites took longer than at the CS-treated sites. Regarding pain, the treated sites exhibited a reduction in discomfort compared to the control sites. Moreover, the CS-treated sites demonstrated enhanced healing on both the first and third postoperative days[75]**.** Another study of Efeoğlu assesses the effects of CS and surgical, topical hemostatics on patients with cirrhosis. The study included 50 cirrhosis patients. A double-blind, randomized study was carried out. The patients were classified based on the type of cirrhosis. The trauma score, bleeding time, and correct bleeding time were calculated for both groups during postoperative reviews. The patients were contacted by phone call after 5 hours, 10 hours, and twice daily for the next 5 days. This communication was used to check for complications or bleeding. Each group had a total of 40 teeth extracted. There were no statistically significant differences found, particularly concerning bleeding time and the other parameters[76]**.** In another study, Pippi *et al*. conducted a randomized controlled trial (RCT) to examine the efficacy and safety of CS-derived hemostatics for bleeding control in post-extractive sockets in 20 patients in the field of oral surgery[77]**. Table (2)** Studies of CS hemostatic effect.

Table 2: Studies of chitosan hemostatic effect.

Polymer	**Dosage form**	**References**
Carboxymethyl chitosan	Hydrogel	[60]
Chitosan	Nanofiber	[61]
Chitosan and Carboxymethyl chitosan	Solution	[62]
Chitosan	Solution	[63]
Quaternized chitosan and phosphorylated chitosan	Hydrogel	[64]
Chitosan	Cellulose-based gauze	[65]
chitosan/alginate complex	Lyophilized foam and impregnated gauze	[66]
Chitosan	Chitosan-based dressing	[67]
Chitosan	Chitosan-based dressing	[68]
carboxymethyl chitosan	Foam dressing	[69]
N-alkylated chitosan	Powder	[72]
N-alkylated chitosan	Hemostatic dressing	[73]
Chitosan	Chitosan-based membrane	[74]
Chitosan	Hydrogel dressing	[57]
Chitosan	Chitosan-based dressing	[75]
Chitosan	Chitosan-based dressing	[76]
Chitosan	Chitosan-based dressing	[77]

Analgesic effects

An analgesic is a substance or treatment that reduces pain. Approximately half of the drugs used to treat inflammation produce analgesics that relieve pain. It has several promising biomedical applications[78]**.** Some scientists have previously documented that both chitin and CS, as well as their derivatives, have an analgesic effect on inflammatory pain**.** The analgesic effect of CS was investigated by numerous researchers. Okamoto *et al*. intended to assess the analgesic properties of chitin and CS in mice using the acetic-acid-induced writhing test, a method commonly used in the development of analgesic drugs. This study showed that the chitin particles absorbed bradykinin more than the CS particles. This results suggest that the main analgesic effect of CS is the absorption of proton ions released in the inflammatory particles, while that of chitin is the absorption of bradykinin[79]**.** In another study, Huang *et al*. aimed to evaluate the analgesic and wound-healing effects of CS and carboxymethyl CS on scalded rats, where the concentration of bradykinin and 5-hydroxytryptophan was detected by assaying enzyme-linked immunosorbent. These findings indicated that carboxymethyl CS reduced the concentration of algogenic substances, resulting in analgesia. During the whole recovery process, the hydroxyproline concentration in CS and carboxymethyl CS group was significantly higher than that of control. In conclusion, carboxymethyl CS showed significant analgesis and wound-healing promotion effect, but CS only showed wound-healing promotion effect [80].

Traditional rat pain and inflammation models were employed by Adnan *et al* to investigate the analgesic and anti-inflammatory properties of CS and its derivative, O Carboxymethylated CS (O-CMC). Furthermore, results of anti-inflammatory properties exhibited that O-CMC inhibited inflammation induced by carrageenan in hind paw of rat which demonstrated O-CMC has a remarkable anti-inflammatory activity. Analgesic activity of O-CMC also exhibited an elevated and persistent pain reaction time for hot plate that confirms analgesic activity of O-CMC[81]. Another investigation, Putri *et al*. aimed to assess the analgesic activity of CS in arthritic rats. To sum up the results of research on the analgesic activity of CS in Sprague Dawley rats induced by Complete Freund's Adjuvant (CFA) as a model of arthritis rats, CS at 50 mg and 100 mg/200 g of rat body weight can be used as analgesics in CFA-induced arthritic rats with a decreased percentage of pain response and is higher compared to diclofenac sodium [82]**.**

In their study, Asad *et al* intended to assess the analgesic properties of chitin and CS via an acetic-acid-induced writhing test in mice, revealing a significant reduction in writhing behavior following the chitin and CS extract. These findings indicate the potential of using chitin and CS derived from termites and Periplaneta americana as natural anti-inflammatory compounds, implying prospective uses in anti-inflammatory, antipyretic, and analgesic capabilities [83]**.** Yet another survey by Hu *et al*. examined the impact of pain relief on the injured sciatic nerve by co-transplanting olfactory ensheathing cells (OECs) with CS, a biological tissue engineering material. OECs+CS transplantation could significantly relieve pain, and the analgesic effect was stronger than that of OECs transplantation alone. These data reveal that OECs+CS have a better analgesic effect in relieving neuropathic pain induced by sciatic nerve injury, and provide a new therapeutic strategy for pain treatment[84]**.** Furthermore, Rahmani *et al*. aimed to determine the effect of CS mouthwash 0.5% on pain relief and ulcer size in recurrent aphthous stomatitis (RAS). CS mouthwash is effective on pain relief and reducing ulcer size of minor aphthous stomatitis and this effect is almost the same as Triamcinolone mouthwash [85]**.** Finally, Nguyen et al. aimed to evaluate the most recent techniques for synthesizing CS hydrogels as an effective anti-inflammatory and analgesic drug delivery system. In order to offer a thorough examination of anti-inflammatory CS hydrogel, the properties of the material, including pH sensitivity, temperature sensitivity, electric sensitivity, and magnetic strength, are each examined [86]**.**

Clinical studies

In clinical studies, CS was investigated as an analgesic in the dental field. Zeza *et al*. reported that using CS-modified brushing resulted in a better periodontal condition in 15

patients in the field of periodontology and implantology [87]. In addition, research has demonstrated that CS brushing can alleviate clinical symptoms of per-implant inflammation, bleeding during probing, and bone level stabilization [88]**.** In comparison to the bicarbonate oral rinse, Lopez-Lopez *et al*. assessed the properties of the same gel from the most recent reviewed study (chlorhexidine, dexpanthenol, allantoin, CS gel). The researchers conducted this randomized controlled trial (RCT) on 47 patients and discovered that the gel patients group achieved superior results in managing pain and inflammation following dental surgery than the bicarbonate rinse group[89]**. Table (3)** summarizes the applications of CS in analgesic effects.

Wound healing

Wound healing is a complex physiological process that repairs tissue integrity. The four major physiological stages are hemostasis, inflammation, proliferation, and tissue remodeling[90]. Because of its healing properties, CS is utilized as an excellent wound dressing in a variety of forms. CS dressings are biocompatible, biodegradable, and promote wound healing. It is used as a dressing due to its strong tissue adhesive properties [91]. Numerous studies have recommended CS as a wound-healing agent and recognized the potential of CS and its derivatives as effective wound-dressing [55]**.** CS can be converted into nanofibers, which have a greater potential for wound healing and drug delivery applications than CS nanoparticles. CS nanofibers have been shown to have efficient properties such as wound healing, improved hemostasis management, cell proliferation, angiogenesis promotion, drug absorption capacity, scaffold integration, blood biocompatibility, and enhanced immune regulation [92]**.** Abuelella *et al*. utilized polyelectrolyte nanoparticles composed of two natural, biodegradable polymers CS and hyaluronic acid to deliver the non-steroidal anti-inflammatory drug etoricoxib to deeper skin layers. This approach minimizes systemic toxicity while enhancing the drug's therapeutic effectiveness, particularly in the treatment of irritant contact dermatitis [93]. In another study, Shen *et al*. successfully developed and created injectable multifunctional Schiff base cross-linked with gallic acid modified CS (CSGA)/oxidized dextran (ODex) hydrogels [94]. These hydrogels exhibited excellent self-healing, porous structure, injectable properties, tissue adhesiveness, and adjustable mechanical properties for the disease characteristics of combined radiation and burn injury (CRBI).

Through neutralization and the utilization of sodium hydroxide as a crosslinker, Elangwe *et al*. created physically crosslinked CS/pullulan hydrogels. They also examined the impact of various CS and pullulan volume ratios on the hydrogels' mechanical, physical, and tissue adhesive properties. Potential applications in medicated wound dressings and drug delivery were explored through the investigation of the capacity to release antimicrobial agents, including gentamicin [95]**.** In another study, Sanmugam *et al*. utilized advanced analytical techniques to assess the physicochemical, mechanical, and biological properties of CS-CeO2 combined nanotitanium dioxide (TiO2) complex-loaded polycaprolactone (PCL) nanohybrid (CS-CeO2/TiO2/PCL) scaffolds prepared using the casting method. When compared to CS-CeO2, the CS-CeO2/TiO2/PCL nanohybrid scaffolds exhibited superior mechanical properties. The swelling ability and degradation profiles of CS-CeO2/TiO2/PCL confirmed its significance in terms of wound exudate absorption [96].

Cefotaxime sodium (Cef.Na)-loaded green synthesized AgNPs were integrated into a bio-inspired natural hydrogel's three-dimensional structure. The hydrogel's CS and collagen (COL) components worked together to prevent microbial infiltration at the wound site while also promoting connective tissue formation [97]**.**

Table 3: Studies of chitosan analgesic effect.

Polymer	Dosage form	References
Chitosan	Suspension	[79]
Chitosan and carboxymethyl chitosan	Solution	[80]
O-Carboxymethylated chitosan	Solution	[81]
Chitosan	Suspension	[82]
Chitosan	Solution	[83]
Chitosan	Catheter	[84]
Chitosan	Mouthwash	[85]
Chitosan	Hydrogel	[86]
Chitosan	CS-modified brushing	[87]
Chitosan	Toothbrush	[88]
Chitosan	Gel	[89]

Clinical studies

CS dressings (Hyphecan®) have been revealed in clinical studies to be effective and simple to apply, maintain, and remove following healing. Stone *et al*. used CS to promote the healing of the split skin graft donor site. Over seven months, eleven female and nine male patients participated in the study. CS dressings were compared to commercial alginate dressings (Kaltostat®) and silicone net gauzes (Mepitel®). As controls, half of the wound was dressed with a Kaltostat® or Mepitel®, and the other half was dressed with CS. The CS dressings were simple to remove, resulting in less pain for the patient, whereas the Kaltostat and Mepitel dressings adhered to the donor site. On day 11, CS biopsies revealed a dermis rich in glycosaminoglycans and capillaries, as well as more dermal nerves than the control dressings. There were no infections or other negative reactions at the split skin donor site [98]**.** An additional study on 35 burn patients found that the CS dressing and Kaltostat® had comparable healing times [99]**.** Furthermore, Kratz *et al*. examined the influence of CS-heparin membranes on the rate of wound healing in human skin. Even after 15 days, the donor untreated sides demonstrated incomplete re-epithelialization. Conversely, the CS-heparin complex exhibited complete and rapid re-epithelialization after 12 days [100]**.** In another study, Biagini *et al*. utilized freeze-dried N-carboxybutyl CS pads to provide soft pads to the donor sites of patients undergoing plastic surgery to facilitate the regeneration of ordered tissue [101]. Compared to control donor sites, it was discovered that the dermal level exhibited improved histoarchitectural order, better vascularization, and the absence of inflammatory cells. Conversely, the epidermal level reported fewer aspects of Malpighian layer proliferation. Therefore, it was proposed that N-carboxybutyl CS induces the formation of cutaneous tissue that is consistently organized and diminishes anomalous healing. Furthermore, Valentine *et al*. conducted a randomized controlled study to assess the effectiveness of a CS/dextran gel on wound healing and hemostasias following endoscopic sinus surgery [102]. The study covered 40 patients who received endoscopic sinus surgery for chronic rhinosinusitis. The CS/dextran gel exhibited rapid hemostasis, with a mean time of 2 minutes, as compared to the control groups. The CS/dextran gel exhibited significantly fewer adhesions than the control

at all time points. Nevertheless, there was not a significant difference between the control and CS/dextran gel in terms of granulation tissue formation, infection, mucosal edema, or crusting. Clinical observations revealed that CS dressings based on policaju® resulted in greater wound contraction and scar tissue synthesis compared to controls [103]. **Table (4)** summarizes the applications of CS in wound healing effects.

Conclusion

CS has significant potential in wound management due to its antimicrobial, hemostatic, and analgesic properties. Its ability to inhibit microbial growth, promote hemostasis, and alleviate pain makes it an attractive candidate for advanced wound dressings. The biopolymer's multifunctional properties, combined with its biocompatibility and biodegradability, provide a promising candidate for developing new therapeutic approaches to wound care. Future research should focus on optimizing CS formulations and investigating interactions with other bioactive materials to improve wound healing outcomes and reduce complications such as infections and excessive scarring.

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الكيتوزان: بوليمر حيوي متعدد الوظائف لتعزيز ألتئام الجروح من خلال خصائص مضادة للميكروبات ومضادة للنزيف ومسكنة للألم، مدعومة بالأدلة الاكلينيكية

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التئام الجروح عملية فسيولوجية معقدة تعمل على إصلاح سلامة الأنسجة من خلال مراحل تشمل وقف النزيف والالتهاب والانتشار وإعادة البناء. والهدف الأساسي من علاج الجروح هو تجنب العدوى والحد من تطور الأنسجة الميتة وتسريع عملية الشفاء والحد من تكوين الندبات ومن هنا تبدأ الدراسة على الكيتوزان وهو بوليمر حيوي طبيعي معروف بخصائصه الفريدة المضادة للميكروبات ومانعة للنزيف ومسكنة للألم، ويعمل كعامل حيوي نشط في العناية المتقدمة بالجروح. ويتناول هذا الاستعراض تركيب الكيتوزان وخصائصه المختلفة، إلى جانب تطبيقاته المستقبلية في علاج الجروح، وفاعلياته كمضادات للميكروبات ووقف النزيف والتأثيرات المسكنة والأبحاث السريرية الاكلينيكية ذات الصلة. كما يُظهر نشاطًا مضادًا للميكروبات ضد البكتيريا والطحالب والفطريات. وقد تعززت إمكاناته في وقف النزيف من خلال التعديلات الكيميائية وخصائصه المسكنة للألم، مما يعزز راحة المريض أثناء مرحلة التعافي.