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WOUND DRESSING APPLICATION OF CHITOSAN-BASED NANOMATERIALS

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ABSTRACT

This review article was set out to investigate chitosan as a component of wound dressings. The approximation method is the one used in this review. Relevant articles were found by searching for keywords like "Chitosan", "Wound Healing", and "Biomedical Application" in national and international journals databases like Scopus, PubMed, and Google Scholar. The articles cannot be a review work and must have been published in national and international journals during the last ten years. A total of 29 research articles which investigated chitosan's application as a material for wound dressings were taken up for the review.

Chitosan-based products, such as nanofibrous membranes, composite sponges, polyelectrolyte

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complexes, and composites, are produced by combining chitosan with various polymers, ions, and other materials. These materials are used to create topical preparations such as membranes, fibers, sponges, films, and gels. The modified chitosan preparations attributed to improve the wound healing process in a better way. This article gives a general overview of several chitosan-based products utilized in healing wounds and their benefits.

Keywords: Chitosan, Wound care, Wound healing, Bandaging, Biomedical industry.

Introduction

The epidermis, dermis, and subcutaneous tissue make up the skin [1]. The first line of defense against potentially dangerous external stimuli on the human body's surface is the skin [2]. As a result, skin injuries—from minor cuts to chronic wounds—are extremely prevalent [3]. A wound is a flaw or breach in the skin that is brought on by physical or thermal harm, the existence of an underlying physiological or medical disease, or both [4]. Wound healing is a biological process which takes place in the human body. Hemostasis, inflammation, proliferation, extracellular matrix synthesis, and tissue maturation are the four stages of wound healing [5]. Minor wounds on the epidermis may normally heal on their own, but major wounds can hinder the immune system from being able to heal the skin. External infections can infect a lesion at any point throughout the healing process, necessitating higher-level clinical care that is more expensive in terms of both money and resources [6]. Over the course of the investigation, chronic wounds became more common overall. For instance, from 2014 to 2018, there was an increase in the number of chronic wound cases in Northern China, and the average hospital stay was 13 days [7]. It has been established that the rising incidence of delayed healing conditions, especially the healing of acute and chronic wounds, has a negative economic impact on society [8]. Researchers have a pressing need to create novel advantageous and effective wound dressing materials to overcome this problem.

Materials for wound dressings are mostly made of biopolymers and synthetic polymers. Biopolymers are a useful material for wound healing processes due to their favorable biocompatibility, non-toxicity, biodegradability, and ease of availability. Biopolymers, on the other hand, have subpar mechanical properties, which is why they are frequently cross-linked with synthetic polymers to improve them [9]. Because of its good physicochemical qualities and biological properties, biocompatibility with human tissues, biodegradability, and antimicrobial activity, chitosan has been recognized as one of the possible choices for wound dressing materials [10]. This review's objective was to investigate various chitosan-based materials which have been applied as bandages for wounds and employed in a variety of treatments.

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Methodology

The approximation method was employed in the writing of this article. In order to conduct a literature review, the websites of national and international publications, including Scopus, PubMed, and Google Scholar, were searched using the keywords "Chitosan," "Wound Healing," and "Biomedical Application." Books and research articles that were published in National and International journals in the last ten years were referred for the preparation of this article, without the inclusion of review articles. The search turned up 39 items, however after filtering 10 were found to be review articles. 29 articles that examined the use of chitosan as a material for wound dressings were ultimately chosen for this evaluation. Eleven articles, one for each area of the evaluation, served as supporting components.

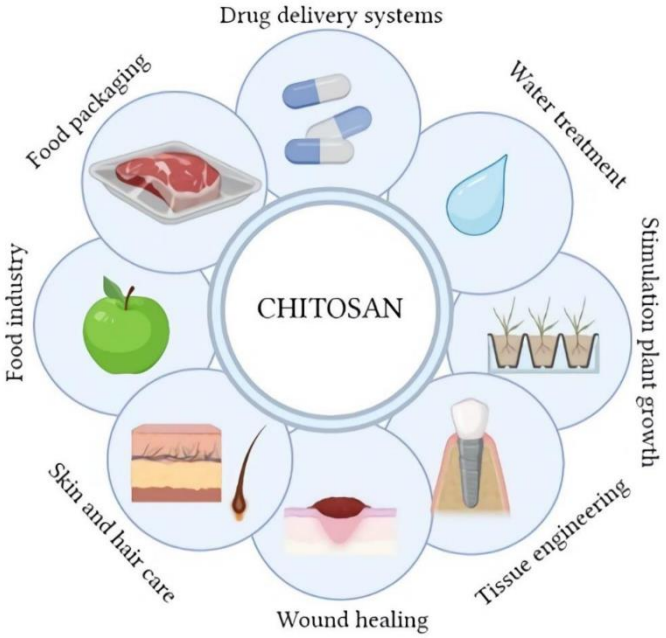

Figure 1: Applications of Chitosan

Discussion

Ideal qualities of materials used in wound dressings

The components used to create wound dressings, such as hydrocolloids, alginates, and hydrogels, are commonly categorized. They are available as foam sheets, gels, and thin films [4]. To qualify as the perfect material for wound dressing, a material must meet several criteria. It must have good moisture and air permeability, be non-toxic, non-irritating, biodegradable, have antimicrobial qualities. In order to avoid wrinkles, it needs also be mechanically strong [11].

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Characterization of chitosan

Numerous poly-(beta-1-4) N-acetyl-D-glucosamine compounds are encapsulated by chitosan [12]. Deacetylating chitin yields the polymer known as chitosan. It has an amino group and both primary and secondary hydroxyl groups at the C-2, C-3, and C-6 locations, making up its three principal reactive functional groups (fig. 2). Fabrication of chitosan into films, scaffolds, hydrogels, fibers, etc. is possible [13].

Chitosan is the second most prevalent natural biopolymer and is frequently found in the cell walls of fungi and the shells of marine crustaceans. With a molecular weight which ranges from 300 to over 1000 kDa, chitosan is quite dense. In aqueous solutions above pH 7, chitosan is insoluble in its crystalline state [15]. Chitosan's limited pH solubility and poor mechanical characteristics can be improved via covalent crosslinking. Ionically crosslinked chitosan hydrogels have a wider range of possible applications than covalently crosslinked chitosan hydrogels because they are more sensitive to pH changes in terms of swelling [16].

Chitosan's mechanism for healing wounds

Chitosan works to treat wounds in three primary ways: hemostatic, antibacterial, and tissue healing process [17]. The crucial stage in the healing of a wound is hemostasis. Chitosan can boost hemostatic effects, according to recent investigations [18]. Red blood cells with negative charges are drawn to the positively charged chitosan molecules. The chitosan's hemostatic action was initiated by this electrostatic attachment to blood cells [19] via adsorbing plasma proteins and signaling thrombin, a clotting promoter, chitosan improves platelet adhesion and aggregation (fig. 3). They do this via increasing the expression of the membrane receptor glycoprotein IIb/IIIa (GPIIb/IIIa).

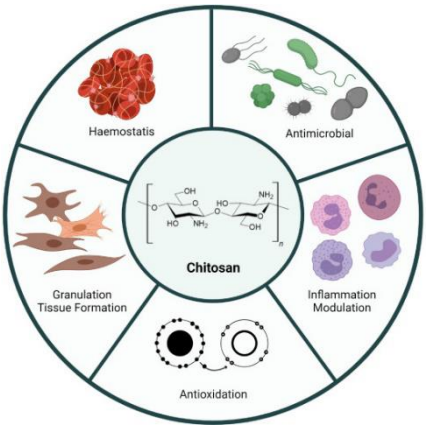

Figure 2: Chitosan for skin Wound Healing

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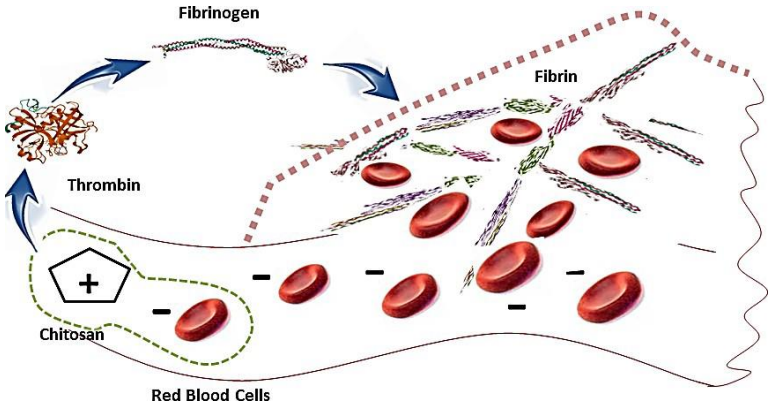

Figure 3: Hemostatic mechanism of Chitosan in wound healing [18–20]

Due to its excellent antibacterial qualities, chitosan is used in wound healing treatments in addition to its hemostatic effect [21]. When chitosan is dissolved in an acidic aqueous solution, the NH_2 groups of high chitosan will protonate to-NH_3^+ cations [22]. As a result, NH_3^+ and the lipopolysaccharides on the cell membrane of Gram-negative bacteria or the teichoic acids on the cell membrane of Gram-positive bacteria will interact electrostatically. As a result of these interactions, the bacteria will develop an uneven distribution of negative charges, which will finally result in cell lysis [23].

In some situations, people may experience difficulties with wound healing problems or even chronic wound disorders. Since these issues require long-term care, the cost of healthcare will likewise rise [24]. The researchers consequently concentrated on creating readily available natural materials for use as wound-dressing material [25]. It has been demonstrated that the biocompatible substance chitosan is non-toxic to live cells and tissues. Fibroblasts, keratinocytes, hepatocytes, as well as myocardial and endothelial cells, all have been used in the *in-vitro* testing of these substance [26]. Inflammatory cells, macrophages, and fibroblasts are stimulated by chitosan, and this can lessen the inflammatory stage of the wound-healing process [27].

Chitosan-based products in the treatment of wounds

Chitosan has been used as the foundation for several wound-healing preparations, including gel, film, membranes, sponges, and fibers (fig. 4). Chitosan can combine with graphene oxide to generate a nanofibrous membrane (CS-GO), whereas silk fibroin produces CS-SF nanofibers. It will be able to create the porous sponge-like structure when silver is present.

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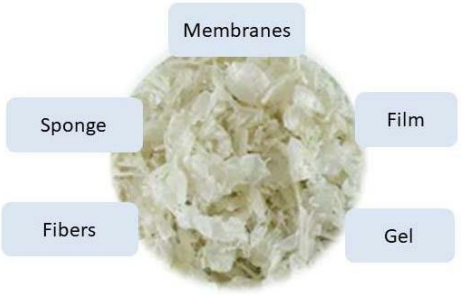

Figure 4: Application of chitosan in wound healing preparations [10,28–36]

Nano fibrous membranes for CS:GO

Chitosan (CS) and graphene oxide (GO) can work well together to create nanocomposites that have high mechanical properties, bioactivity, and biocompatibility. Due to the presence of hydrogen bonds, CS is constrained by its poor flexibility and solubility in most of the standard solvents. In order to compensate for CS's lack of electro-spinnability and create antibacterial CS-GO nanocomposite fibrous membranes, flexible and biocompatible polymers are frequently added. Numerous benefits exist for CS:GO based nanocomposite wound dressings, including acceptable mechanical strength, anti-inflammatory qualities, and tissue adhesion traits. Contrary to previous described systems, the electron transport in CS-GO nanocomposites is constrained [12].

Table1: Applications of chitosan-based materials in wound healing

Materials	Physical form	Advantages	References
CS-GO Nanofibrous Membranes	Nanofibrous Membranes	Adequate mechanical strength, anti-inflammatory properties and tissue adhesive characteristics.	[10]
CS-SF Composites	Nanofibers	Antibacterial activity of the material against Gram-negative bacteria and improved cell attachment and proliferation.	[37]
CS-AgSD Composites Sponge	Sponge	Excellent antibacterial performances on *E. coli, C. albicans, S. aureus,* and *B. subtilis.*	[28]
CS-nAU	Film	High anti-microbial activity towards *Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa, Candida albicans*, and a multi-drug resistance strain from *Pseudomonas aeruginosa*.	[28]
CS-ZnO	Nanoparticles	High antimicrobial activity on gram-positive bacteria.	[38]
CS–alginate polyelectrolyte complex (PEC)	Membrane	Good mechanical properties, capable of facilitating the remodeling of scar tissue, good anti- inflammatory properties.	[29]
CS-Gelatin	Gel	Good wound dressing materials for liver tissue, efficient in inducing fibrin formation and vascularization.	[30]

CS-Titanium Oxide Composite	Membranes	Better mechanical strength, and improved crystallinity and flexibility, excellent antibacterial activity towards *Staphylococcus aureus*.	[31, 32]
CS-Sodium Alginate	Film	Accelerated healing of incision wounds, excellent remodeling phase with organized thicker collagen bundles and mature fibroblasts; nontoxic toward fibroblast cells.	[31]
Cs-BC	Membranes	Maintain at suitable moisture content for wound healing applications, good mechanical properties and cytocompatibility, increased the growth inhibition against *E. coli and S. aureus*.	[33]
CS-hyaluronic acid nanosilver Composite	Sponge	Ideal wound dressing in terms of swelling, porosity, biodegradation, hemostatic potential and was effective in reducing the in vitro growth of *S. aureus, E. coli, MRSA, P. aeruginosa and K. pneumoniae*.	[34]
CS-PVA and Lignin	Hydrogel	Good bactericidal activity, antioxidant activity, high mechanical strength, and large tensile deformation.	[35]
hmCS-OD	Hydrogel	Good hemostasis, antibacterial activity, tissue adhesion, cytocompatibility, and accelerated wound healing.	[36]

CS-SF composites nanofibers

In order to create chitosan/silk fibroin nanofibers for usage in bone tissue formation and wound-dressing applications, electro spinning was performed (fig. 5). A composite nanofibrous membrane with higher mechanical resistance and a larger diameter of nanofibers was created when silk fibroin was added to chitosan. The antibacterial activity of the material against Gram-negative bacteria was enhanced by the addition of Chitosan to silk fiber. The chitosan/silk fibroin combination increased cell attachment and proliferation, according to the biochemical tests [16, 37].

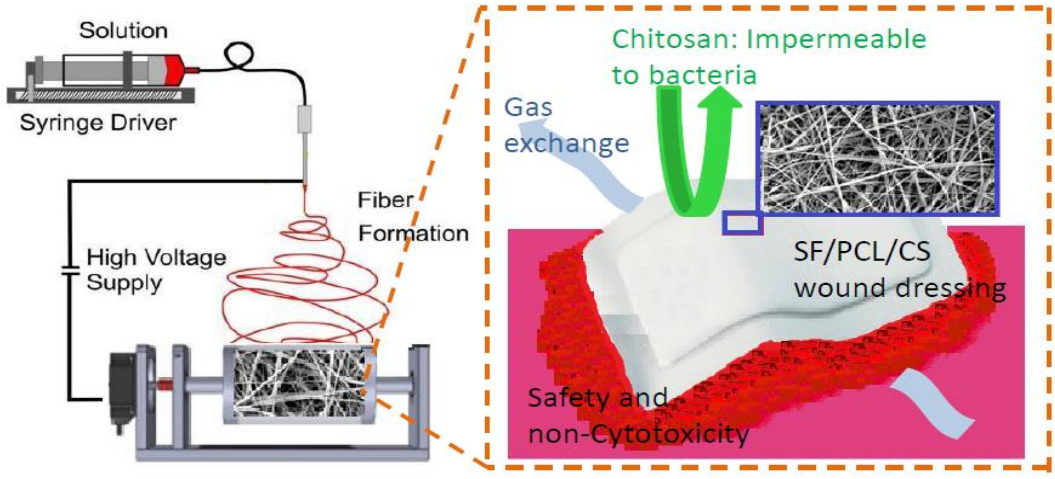

Figure 5: CS-SF composites nanofibers

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CS-AgSD composites sponge

The surface characteristics of the antibacterial chitosan/silver sulfadiazine (CS/AgSD) composite sponges were characterized using XRD, FTIR, and SEM methods. The findings demonstrated that CS/AgSD composite sponges had a high porosity and swelling ratio, whereas CS sponge's porosity decreased as the AgSD percentage in the sponges increased (fig. 6). Testing of the CS/AgSD sponges antibacterial and cytotoxic properties revealed that they had outstanding antibacterial activity against *E. coli*, *C. albicans*, *S. aureus*, and *B. subtilis*. Cytotoxicity studies have revealed that CS/AgSD sponges show very little cytotoxicity against bacteria. [39].

Chitosan silver (CS-Ag) film

Escherichia coli, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Candida albicans*, and a multidrug-resistant strain of *Pseudomonas* are all inhibited by quaternized chitosan films and silver-loaded chitosan nanocomposites. After 24 hours, the viability of human cells cultivated on Quaternized Chitosan (QC) control films was about 84%. However, as silver nanoparticle (AgNP) concentrations decreased, cell survival increased. AgNPs at high concentrations had greater antibacterial activity, but they were hazardous to human cells as well. As a result, scientists have discovered that silver nanoparticles with 0.125% Ag more useful for applications as wound dressings [28].

CS-ZnO NP

The solution mixing and casting method was used to combine and cast ZnO nanoparticles with CS modifications into a film. When compared to the unmodified ZnO nanoparticles, the resultant films showed an increase in porosity, hydrophilicity, water absorption and water vapor transmission rate, oxygen permeability, and biodegradability. Antibacterial activity of nanocomposites against *Staphylococcus aureus* and *Micrococcus luteus* was investigated in this work. In a study of wounds in living beings, CS-ZnO-treated wounds healed more quickly than gauze-covered wounds, and the nanocomposite also encouraged the formation of new collagen and re-epithelialization [38].

While standard gauze was still in a critical inflammatory phase beneath the scab, chitosan-alginate polyelectrolyte complex (PEC) APEC membranes successfully presented the mature epidermis with a keratinized surface of normal thickness and decreased inflammation in the dermis. By speeding up collagen synthesis and compressing collagen fibers into bigger bundles, chitosan-alginate PEC membranes also appeared to aid in the remodeling of scar tissue. 21 days after surgery, a great remodeling phase with well-organized, thicker collagen bundles and mature

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fibroblasts was seen [29].

Gelatin–chitosan gel

A 40% (w/v) gelatin solution was created by dissolving 40 g of gelatin in 100 ml of distilled water using a magnetic stirring bar. This solution was then incubated at 80 °C for 2 hours to generate the gel. A 2% (w/v) chitosan solution was created by dissolving 2 g of chitosan in an aqueous solution of 2% acetic acid. For a 20:1 weight concentration ratio of the two polymers, the 40% gelatin solution and the 2% chitosan solution were combined at around 40 °C for 6–8 hours according to a set mass ratio (1:1, v/v) (fig. 7). Results showed that as compared to the gelatin/chitosan gel, the gelatin gel had a considerably lower antigenic reaction and a faster rate of disintegration. Comparatively to the area around single-polymer gels, the gel's surroundings had more advanced cell accumulation and infiltration. In comparison to single polymer gels, the gelatin/chitosan gel promoted fibrin information and vascularization more quickly [30].

Chitosan/titanium oxide (TiO2) composite

Through stimulating the expression of fibroblast markers and exhibiting strong antibacterial activities, this study showed that the CS/TiO2 membrane had growth-promoting effects on L929 cells. By activating the fibroblast signaling pathway during the natural healing cascade, this substance may also speed up the healing process. The L929 cells were cultivated on the CS/TiO2 composite membrane, and the proliferation, survival, and general functional integrity of the cells were further validated by the gene/protein expression profiling of fibroblast-associated markers. Additionally, the CS/TiO2 composite membranes showed improved antibacterial action against *S.aureus* [32, 40].

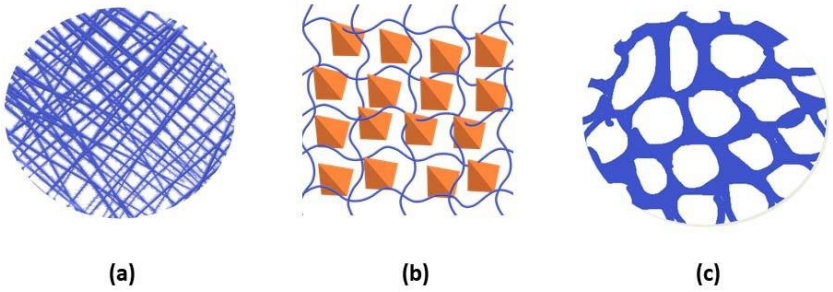

Figure 6: Chitosan based structure: fibers (a) polyelectrolyte complex/composite (b)and sponge (c) [10,28,29,32,34,37].

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(a) (b)

Figure 7: Preparation of Chitosan-based: gel (a), and film/membrane (b) [28,30,31,35]

Sodium alginate/CS-based films

Using male Rattus norvegicus albinus, Wistar strain, the safety and effectiveness of sodium alginate/CS and glycerol films for low-level laser therapy in cutaneous burn wound healing were assessed *in-vivo.* Treatment was given for seven days. Results revealed that treated cellulose films had more blood vessels and a higher rate of epithelization than untreated cellulose films [31].

Bacterial cellulose-chitosan membranes

In a rat full-thickness wound model, the wound healing abilities of bacterial cellulose generated by *Acetobacter xylinum* and its composite with chitosan were assessed. Transparent films, hydrocolloid from 3M tegaderm, BC and BC-Ch membranes were used (fig. 8). *In-vivo* research shows that wounds treated with BC-Ch membrane not only healed more quickly, but also saw faster epithelialization and regeneration than wounds treated with BC or tegaderm. The findings of this study suggest that BC-Ch membranes should be regarded as a crucial component of wound care [33].

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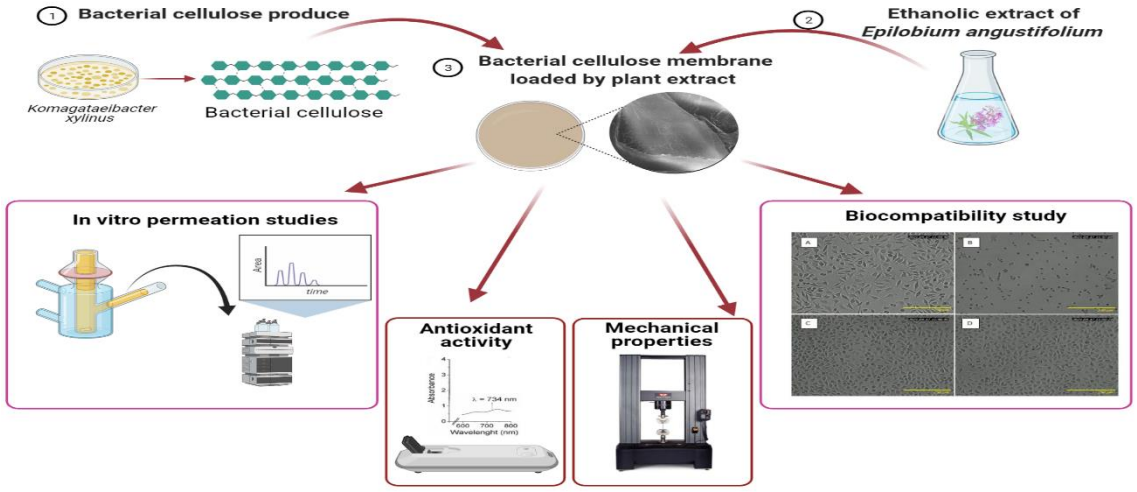

Figure 8: Bacterial cellulose-chitosan membranes

Chitosan-hyaluronic acid/nano silver composite

In order to create antimicrobial sponges that may be used as a dressing for wounds with drug-resistant bacteria, CS, hyaluronic acid, and AgNPs were combined. A flexible and porous structure was produced by homogeneously combining CS, hyaluronic acid, and AgNPs and then freeze drying the mixture. Because it is biodegradable and possesses hemostatic potential, this type of structure exhibits a swelling tendency that is perfect for wound dressing applications. Then, it has been shown that sponges with Ag incorporation are efficient at reducing the growth of *S. aureus*, *E. coli*, Methicillin-resistant *Staphylococcus aureus* (MRSA), *P. aeruginosa*, and *K. pneumoniae in- vitro* [34].

Chitosan-PVA and lignin

A brand-new lignin-chitosan-poly (vinyl alcohol) hydrogel exhibits good biocompatibility, antibacterial activity, and significant tensile deformation. In order to increase the mechanical strength and slow the rate of degradation of a hydrogel comprising both lignin and chitosan, sulfonate groups were added in the chemical structure of lignin to create ionic connections with amino groups in chitosan. Further research using mice models showed that this composite hydrogel can maintain a moist healing environment and facilitate faster healing than a composite containing only chitosan [35].

Hm CS-OD Injectable hydrogel

Deionized water (DIW), acetic acid (49.5:0.5, v/v), and ethyl alcohol (25, v/v) were combined to

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dissolve a total of 1g of CS, and then 69.5 L of dopamine (DA) was added dropwise to the mixed solution. A chemical reaction between hydrophobically modified chitosan (an organic molecule) and oxidized dextran produced an injectable hydrogel for use in wound dressings. A gel was produced as a result of this reaction, and it displayed several properties, including hemostasis (the cessation of bleeding), antibacterial activity (the prevention or reversal of bacterial growth), tissue adhesion (the adhesion of cells to a surface), cytocompatibility (compatibility with living cell sorting tissues), and expedited wound healing [36].

Conclusion

Chitosan, a natural product offers outstanding biological qualities as wound dressing material. As already mentioned, numerous researches have been demonstrated that chitosan has hemostatic and antimicrobial properties. Additionally, it promotes the body's own healing mechanism. However, issues with its mechanical properties and restricted solubility limit its use as a wound dressing material. To overcome these drawbacks, numerous researchers have undertaken investigations and experiments that involve mixing chitosan with certain compounds. We think that the use of chitosan-based products is an economical answer for the biomedical industry's expanding demand for wound healing techniques. The use of various chitosan-based polymers as wound dressings is currently the subject of more clinical trials for future research.

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