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Review Article

A REVIEW ON CHITOSAN-BASED MATERIALS AS POTENTIAL WOUND DRESSING MATERIALS

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ABSTRACT

This review article aimed to study chitosan as a material based in wound dressing preparation. The method in this review is the approximation method. The articles were obtained from national and international journals such as Scopus, PubMed, and Google Scholar by using the keywords "Chitosan", "Wound Healing", and "Biomedical Application". The inclusion criteria of the article are: national and international journals and books contains chitosan as, published in the last ten years, and not review article. The final articles used in this review are 29 articles that studying the use of chitosan as wound dressing material. The combination of chitosan with some polymer, ion and other materials resulting the chitosan-based materials namely nanofibrous membranes, composites sponge, polyelectrolyte complex, and composites, that used in topical preparation such as membranes, fibers, sponge, film, and gel. Thus, the modified of chitosan wound healing preparation resulting in the improve of healing activity of each preparation from. This review summarizes chitosan application in wound healing. Several studies were proposed the porous structure of chitosan-based materials lead the improvement of healing activity.

Keywords: Chitosan, Wound healing, Wound dressing, Biomedical field

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INTRODUCTION

Skin is composed of the epidermis, dermis, and subcutaneous tissue [1]. Skin is the first line organ in the human surface that protect the internal body from any harmful external factors [2]. Hence, it is so common for skin to get wounds, from an easy-to-heal wound to chronic wounds [3]. A wound is a defect or break in the skin, caused by physical or thermal damage or by the presence of an underlying medical or physiological condition [4]. Wound healing is a biological process in human body. There are four phases in wound healing process: hemostatic, inflammation, proliferation, and the formation of extracellular matrix and the maturation of tissues [5]. Although the epidermis is naturally capable of self-repairing superficial damage, a major wound may cause the immune system to fail in its task of repairing the skin. If a wound becomes infected with external pathogens at any stage of the healing process, it will require higher clinical treatment that will cost more money, time, and resources [6]. Total prevalence of chronic wounds increased over the study period. For example, in Northern China, cases of chronic wounds increased from 0.94% to 2.11% in 2014 to 2018 and the average duration of the hospitalization was 13 d [7]. This increasing case of delayed healing conditions, including acute and chronic wounds healing process, has proven to cause socioeconomic suffering in society [8]. This issue caused the urgent need for researchers to develop new beneficial and efficient wound dressing materials.

Wound dressing materials are mostly obtained from biopolymers and synthetic polymers. Biopolymers has some properties, such as: good biocompatibility, non-toxicity, biodegradability, and readily availability that makes them a suitable material for wound healing process. However, biopolymers have poor mechanical properties which caused these biopolymers are usually cross-linked with synthetic polymers to fix their mechanical properties [9]. Chitosan has seen as one of the potential candidates for wound dressing materials because its characterization, including excellent physicochemical characteristics and biological properties, biocompatibility with human tissues, biodegradability, and antibacterial and antimicrobial activity [10]. The aim of this review is to study the several forms of chitosan-based materials that have been used in wound dressing and and the application this materials in many kind of preparation forms.

Methodology

The method used in the making of this article is the approximation method. The keywords "Chitosan", "Wound Healing", and "Biomedical Application" were used to search the sites of national and international journals such as Scopus, PubMed, and Google Scholar for this literature study. The inclusion criteria of article were: national and international journals and books contains chitosan, published in the last ten years, and not review articles. The search obtained 39 articles, then sreening excluded 10 articles that contains the review article. The final articles selected in this review are 29 articles that studying the use of chitosan as wound dressing materials (fig. 1). The supporting articles for this review were 11 articles that completed of each section in this review.

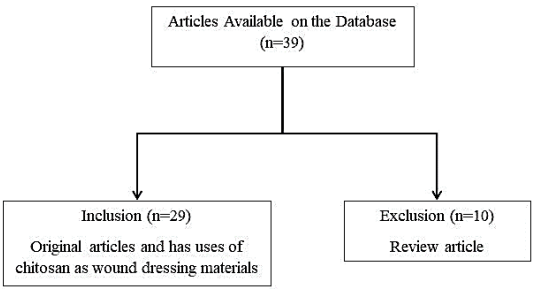

Fig. 1: Flowchart of the methodology used in this review

DISCUSSION

Ideal characteristics for wound dressing materials

Wound dressings are generally classified according to the materials from which they are made, including hydrocolloids, alginates, and hydrogels. They come in the form of gels, thin films, and foam sheets [4]. There are some requirements that have to be fulfilled in order to make a material considered as an ideal wound dressing material. It must be nontoxic, non-irritating, biodegradable, have antimicrobial properties, good moisture and air permeability. It should also have mechanical strength in order to prevent wrinkling [11].

Characterization of chitosan

Chitosan encircles a wide range of poly-(beta-1-4) N-acetyl-D-glucosamine materials [12]. Chitosan is a polymer obtained from the deacetylation of chitin. It has three primary reactive functional

groups: an amino group, as well as both primary and secondary hydroxyl groups at the C-2, C-3, and C-6 positions (fig. 2). Chitosan can be fabricated into films, scaffolds, hydrogels, fibers, etc [13].

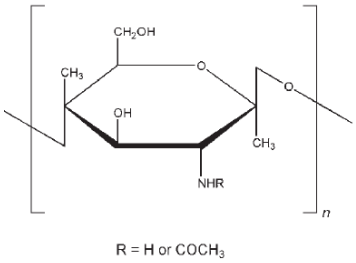

Fig. 2: Chitosan structure [14]

Chitosan is the second most abundant natural biopolymer commonly found in shells of marine crustaceans and cell walls of fungi. Chitosan has a high molecular weight, range from 300 to over 1000 kDa. In its crystalline form, chitosan is insoluble in aqueous solutions above pH 7 [15]. Chitosan can be modified by covalent crosslinking to fix its low solubility in natural pH and low mechanical properties. The swelling sensitivity of ionically crosslinked chitosan hydrogels to changes in pH is greater than that of covalently crosslinked chitosan hydrogels, which extends the potential application of ionically crosslinked chitosan hydrogels [16].

Mechanisms of chitosan in wound healing

There are three main mechanisms of Chitosan in wound healing: haemostatic, antibacterial, and tissue healing process [17]. Haemostatic is the important step in the wound healing process. Recent studies show that chitosan can promote haemostatic effect [18]. The positively charged chitosan molecules attract the negatively charged red blood cells. This electrostatic adhesion to blood cells activated the chitosan's haemostatic effect [19]. Chitosan stimulates platelet aggregation and adhesion by adsorbing plasma proteins and signaling thrombin, which is a clotting promoter enhancing the expression of glycoprotein IIb/IIIa (GPIIb/IIIa), a membrane receptor on the surface of platelets (fig. 3) [20].

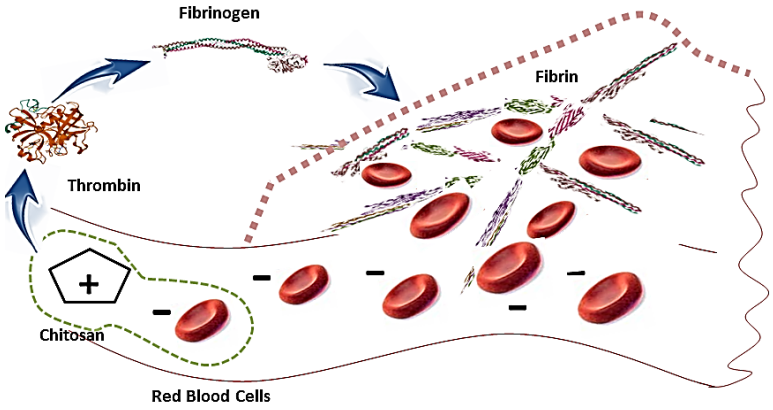

Fig. 3: Haemotatic mechanism of Chitosan in wound healing [18–20]

Beside its haemostatic effect, chitosan is also used in wound healing treatment due to its great antibacterial properties [21]. The NH_2 groups of high chitosan will protonate to-NH_3^+cations when Chitosan is dissolved in an acidic aqueous solution [22]. This will create electrostatic interactions between-$NH_3^+$and lipopolysaccharides of the Gram-negative bacteria cell membrane or the teichoic acids on Gram-positive bacteria. These interactions will cause uneven distribution of negative charges to occur on the bacteria, that will eventually lead to cell lysis [23].

In some cases, individuals may struggle with wound healing disorders and even develop a chronic wound disorder. These problems required a long-time treatment which will also increase the costs for medical care [24]. As a result, the researchers focused on developing easily accessible natural substances for wound-dressing material [25]. Chitosan is a biocompatible material that has been shown to be nontoxic to living cells and tissue. This material has been tested *in vitro* using fibroblasts, keratinocytes, and hepatocytes as well as myocardial and endothelial cells [26]. Chitosan stimulates inflammatory cells, macrophages, and fibroblasts, which can reduce the inflammatory phase in the wound-healing process. This triggers an earlier onset of the proliferative phase [27].

Some applications of chitosan-based materials in wound healing

Chitosan has been applied as a base of some preparation for wound healing, namely gel, film, membranes, sponge and fibers (fig. 4). Chitosan be able to form a nanofibrous membrane with graphene oxide (CS-GO), while the combination with silk fibroin resulting in CS-SF nanofibers. In the presence of silver, be able to form the porous structure called the sponge.

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

CS-GO nanofibrous membranes

The combination of chitosan (CS) and graphene oxide (GO) can complement each other, leading to the preparation of nanocomposites with excellent mechanical performance, bioactivity, and biocompatibility. CS is limited by poor flexibility and solubility in most conventional solvents due to the existence of hydrogen bonds. To produce antibacterial CS–GO nanocomposite fibrous membranes, flexible and biocompatible polymers are often blended with CS to make up for its lack of electro-spinnability. Nanocomposite wound dressings made from CS–GO have multiple advantages, including adequate mechanical strength, anti-inflammatory properties and tissue adhesive characteristics. However, the nanocomposites of CS–GO have limited electron transfer compared to other reported systems [12].

Table 1: 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 remodelling 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, haemostatic 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 haemostasis, antibacterial activity, tissue adhesion, cytocompatibility, and accelerated wound healing.	[36]

CS-SF composites nanofibers

The electrospinning process was used to produce chitosan/silk fibroin nanofibers for use in wound-dressing applications and bone tissue development (fig. 5). The addition of silk fibroin to Chitosan resulted in the production of composite nanofibrous membranes with increased mechanical resistance and an enlarged diameter of nanofibers. The addition of chitosan to silk fibroin promoted the antibacterial activity of the material against Gram-negative bacteria. The biochemical tests showed that chitosan/silk fibroin material improved cell attachment and proliferation [16, 37].

CS-AgSD composites sponge

Antibacterial chitosan/silver sulphadiazine (CS/AgSD) composite sponges were developed, and XRD, FTIR and SEM techniques were used to characterize their surface properties. The results showed that CS/AgSD composite sponges had a high porosity and swelling ratio while the porosity of CS sponges decreased as the AgSD content in the sponges increased (fig. 5). Antibacterial and cytotoxic activities of CS/AgSD sponges were tested and showed that the sponges had excellent antibacterial activity against *E. coli, C. albicans, S. aureus,* and B. *subtilis*. Cytotoxicity tests showed that they had biocompatibility by preferential toxicity to bacterial cells and insignificant cytotoxicity [39].

CS-nAU film

Quaternized chitosan films and silver-loaded chitosan nanocomposites have been shown to inhibit the growth of *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Candida albicans*, and a multi-drug resistance strain from *Pseudomonas aeruginosa*. Human cells cultured in quaternized Chitosan (QC) control films had a viability of approximately 84% after 24 h. However, cell viability increased with decreasing levels of silver nanoparticles (Ag NPs). Although high levels of Ag NPs exhibited higher antimicrobial activity, it also exhibited toxic effects on human cells. Therefore, researchers have found that silver nanoparticles with<0.125% Ag are more effective for wound dressing applications [28].

CS-ZnONP

CS-modified ZnO nanoparticles were mixed and cast into a film using the solution mixing and casting technique. The resultant films displayed an increase in porosity, hydrophilicity, water absorption and water vapor transmission rate, oxygen permeability, and biodegradability when compared to the unmodified ZnO nanoparticles. In this study, the antimicrobial activity of nanocomposites was studied against *Staphylococcus aureus* and *Micrococcus luteus*. A study of wounds healed in living organisms found that wounds treated with CO/CS-ZnO healed faster than those covered with gauze and that the nanocomposite promoted re-epithelialization and collagen deposition [38].

Chitosan–alginate polyelectrolyte complex (PEC)

A PEC membrane successfully displayed the mature epidermal architecture with keratinized surface of normal thickness and subsided inflammation in the dermis, while conventional gauze was still in a serious inflammatory phase under scab. Chitosan-alginate PEC membranes also appeared to facilitate the remodeling of scar tissue by increasing the rate of collagen synthesis and compaction of collagen fibers into thicker bundles. An excellent remodeling phase with organized thicker collagen bundles and mature fibroblasts was observed 21 d postoperative [29].

Gelatin–chitosan gel

To prepare the gel, 40 g gelatin was dissolved in 100 ml distilled water with a magnetic stirring bar and incubated at 80 °C for 2 h to create a 40% (w/v) gelatin solution. Chitosan (2 g) was dissolved in a 2% acetic acid aqueous solution to make 2% (w/v) chitosan solution. The 40% gelatin solution was mixed with the 2% chitosan solution at about 40 °C for 6–8 h according to a fixed mass ratio (1:1, v/v) to obtain a 20:1 weight concentration ratio of the two polymers (fig. 6). Results showed that the gelatin gel had a relatively lower antigenic response and faster degradation rate when compared with the gelatin/chitosan gel. Cell accumulation and infiltration around the gel were more advanced compared to those surrounding single-polymer gels. The gelatin/chitosan gel induced faster fibrin formation and vascularization than did single-polymer gels [30].

Chitosan/titanium oxide (TiO_2) composite

This study demonstrated that the CS/TiO_2 membrane exhibited growth-promoting effects on L929 cells by inducing the expression of fibroblast markers and showing significant antibacterial effects.

Furthermore, this composite could induce an accelerated healing rate by activating the fibroblast signaling pathway during the inherent healing cascade. The gene/protein expression profiling of fibroblast-associated markers further confirmed the growth and survival, and overall functional integrity of L929 cells cultured onto the CS/TiO_2 composite membrane. In addition, the CS/TiO_2 composite membranes showed superior antibacterial activity against *S. aureus* [32, 40].

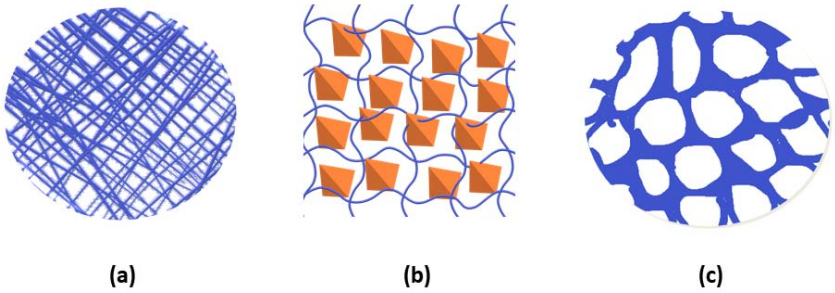

Fig. 5: Chitosan-based structure: fibers (a), polyelectrolyte complex/composite (b), and sponge (c) [10, 28, 29, 32, 34, 37]

Sodium alginate/CS-based films

Safety and efficacy of sodium alginate/CS and glycerol films for low-level laser therapy in dermal burn wound healing was evaluated *in vivo* using male *Rattus norvegicus* albinus, Wistar strain. Treatment was applied for 7 d. Results showed that sodium alginate/CS-based films showed the highest epithelization rate and more blood vessels than untreated, cellulose films [31].

BC-Ch membranes

Wound healing properties of *Acetobacter xylinum*-produced bacterial cellulose and its composite with chitosan were evaluated in a rat full-thickness wound model. BC and BC–Ch membranes, 3M tegaderm hydrocolloid and transparent films were used (fig. 6). *In vivo* study reveals that BC–Ch membranes treated wounds not only healed more rapidly but also epithelialized and regenerated faster than those treated with BC or tegaderm. The results of this study indicate that BC–Ch membranes are to be considered as a very important treatment for wounds [33].

Chitosan-hyaluronic acid/nano silver composite

Antimicrobial sponges composed of CS, hyaluronic acid and Ag NPs were developed using freeze-drying as a wound dressing with drug-resistant bacteria. Homogenous mixing of CS, hyaluronic acid and Ag NPs followed by freeze drying resulted into a flexible and porous structure. This kind of structure presents a swelling behavior ideal for wound dressing applications, it is biodegradable and has hemostatic potential. The nAg-incorporated sponges have proven to be effective in reducing the *in vitro* growth of *S. aureus*, *E. coli*, Methicillin-resistant *Staphylococcus aureus* (MRSA), *P. aeruginosa* and *K. pneumonia* [34].

Chitosan-PVA and lignin

A novel lignin–chitosan–poly (vinyl alcohol) hydrogel shows high mechanical strength and large tensile deformation while displaying bactericidal activity, antioxidant activity, and good biocompatibility. Sulfonate groups in the chemical structure of lignin formed ionic bonds with amino groups in the chemical structures of chitosan, thereby increasing the mechanical strength and reducing the rate of degradation of a hydrogel containing both lignin and chitosan. Analysis of mouse models further demonstrated that this composite hydrogel can maintain a moist healing environment and enables faster healing than does a composite containing only chitosan [35].

hmCS-OD Injectable hydrogel

A total of 1 g CS was dissolved in a mixture of deionized water (DIW)/acetic acid (49.5:0.5, v/v) and ethyl alcohol (25, v/v); then 69.5 µL of DA was added dropwise to the mixture solution. An injectable hydrogel for wound dressing material was made with a chemical reaction between hydrophobically modified chitosan (an organic compound) and oxidized dextran. This reaction created a gel that exhibited several features, including hemostasis (the stoppage of bleeding), antibacterial activity (the prevention or reversal of bacterial growth), tissue adhesion (the adherence of cells to a surface), cytocompatibility (compatibility with living cells or tissues), and accelerated wound healing [36].

Fig. 6: Preparation form of Chitosan-based: gel (a), and film/membrane (b) [28, 30, 31, 35]

CONCLUSION

Chitosan is a natural substance that has excellent biological properties to be a wound dressing material. As discussed above, many studies have proven that Chitosan has haemostatic and antibacterial activity. It also stimulates the natural healing process. However, its low solubility and mechanical properties are issues preventing it from being widely used as a wound dressing material. Many researchers have developed some studies and experiments to fix its limitation, such as combining chitosan with certain materials. We believe that the usage of chitosan-based materials is a cost-effective solution to the biomedical field in wound healing process,

which will be increasing in the future. However, further clinical trials on some chitosan-based materials as wound dressings are conducted for future research.

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Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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