Review Article

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The use of chitosan as a skin-regeneration agent in burns injuries: A review

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Abstract: Chitosan is an amino-polysaccharide, traditionally obtained by the partial deacetylation of chitin from exoskeletons of crustaceans. Properties such as biocompatibility, hemostasis, and the ability to absorb physiological fluids are attributed to this biopolymer. Chitosan's biological properties are regulated by its origin, polymerization degree, and molecular weight. In addition, it possesses antibacterial and antifungal activities. It also has been used to prepare films, hydrogels, coatings, nanofibers, and absorbent sponges, all utilized for the healing of skin wounds. In *in vivo* studies with second-degree burns, healing has been achieved in at least 80% of the cases between the ninth and twelfth day of treatment with chitosan coatings. The crucial steps in the treatment of severe burns are the early excision of damaged tissue and adequate coverage to minimize the risk of infection. So far, partial-thickness autografting is considered the gold standard for the treatment of full-thickness burns. However, the limitations of donor sites have led to the development of skin substitutes. Therefore, the need for an appropriate dermal equivalent that functions as a regeneration template for the growth and deposition of new skin tissue has been recognized. This review describes the properties of chitosan that validate its potential in the treatment of skin burns.

Keywords: burns, chitosan, biomaterial, wound healing, topical treatment

1 Introduction

The increase of the world population has reached the generation of waste in an excessive way. Specifically, in the marine-food industry, by-products and wastes have been generated over the years. Head, scales, shell, bones that increase excessively and affect not only the environment and biodiversity, but also humans. Marine wastes are regularly burned, thrown into landfills or back to the ocean, negatively affecting coastal areas with an unpleasant odor and bacterial contamination during decomposition (1).

Various studies on the elaboration of biological materials for their application in different areas have directed their attention to renewable resources. Chitin is an abundant biopolymer mainly found in marine ecosystems. It is a natural amino-polysaccharide consisting of a linear chain of repeated monomer units of D-glucosamine and N-acetyl-glucosamine, whose content and sequence are variable (2).

Chitosan is obtained through partial deacetylation of chitin by thermo-alkaline hydrolysis of chitin (3), biological-enzymatic (4), and physical methods (5). Chitosan extracted from shellfish residues of crustaceans has gained powerful attention for its potential applications in the mining industry, water treatment and soil leachate (6), the food industry (7), agriculture (8), the cosmetic industry (9), and the textile industry (10). The amino groups allow specific chemical reactions and give important functional properties to chitosan (11), which are responsible for all of its different applications.

In recent years, biodegradable polymers have been recommended for the preparation of coatings for wounds based on their biological properties such as biocompatibility, non irritant and antimicrobial properties, among others (12). Biodegradable polymers, in general, are attractive for tissue engineering. Natural gum polysaccharides (13), bovine type I collagen (14), tilapia skin collagen for the pediatric treatment of burns (15) have reported favorable results for the biomedical sector. Spider silk is also a

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biomaterial recognized for its outstanding mechanical and biocompatibility properties for potential medical applications (16).

In the medical field, tissue engineering has been achieved with the production of advanced bandages for the treatment of acute and chronic wounds, which act in a timely and cost-effective manner. Among these materials are hydrogels, hydrocolloids, gauzes, foams, and fibrous dressings such as alginates and occlusive synthetic materials (17). Coatings for wounds provide a permeable barrier for moisture and oxygen and prevent colonization and proliferation of microorganisms in the wound (18).

Wounds are classified as acute and chronic as a result of a thermal, physical, or chemical injury. Wound healing takes place in five stages: hemostasis, inflammation, migration, proliferation, remodeling, and maturation. The healing periods for acute and chronic wounds are 8–12 days, respectively (19).

The main objective of burn treatment is to improve the healing process including proliferation, granulation, epithelialization, and collagenation (20); from this perspective, the modern concept of wound healing is based on establishing an optimal environment with adequate humidity around the wound, effective circulation of oxygen to favor cell division and tissue regeneration, and a low bacterial density that allows normal movement of epithelial cells, thus accelerating the rehabilitation phase and wound healing (21).

The proper choice of a topical coating to restore the balance of moisture in a wound depends on factors such as the amount of exudate, the anatomic location of the wound, the condition of the surrounding skin, whether a full recovery is expected or not, also should form a rapid film, show a broad antibacterial spectrum and strong antibacterial activity, and be cost effective (22). This study presents a detailed literary review of chitosan as a biopolymer with regenerative capacity in burn injuries, including clinical cases that confirm its therapeutic value.

2 Chitosan

Chitosan is a promising biopolymer in many different areas of science. Structurally, it is an amino-polysaccharide consisting of a linear chain of two repeating monomers of D-glucosamine (deacetylated units) and N-acetyl-D-glucosamine (acetylated units) linked by β -(1,4) glycosidic bonds (3). Chitosan (Figure 1) is composed of less than 20% of β -(1,4)-2-acetamido-D-glucopyranose and more than 80% of β -(1,4)-2-amino-D-glucopyranose (23).

Figure 1: Chemical structure of chitosan.

It is obtained from the alkaline hydrolysis of chitin, one of the most abundant natural amino-polysaccharides extracted from the exoskeleton of crustaceans and insects (24).

2.1 Functional properties

The deacetylated form of chitosan in acidic solutions can be easily processed as powder, paste, gel, membranes, sponges, nanofibers, beads, microparticles, nanoparticles, and nanofibers (25).

The properties of chitosan depend on the range of deacetylation and the distribution of the acetyl groups along its main chain (26). In addition, this biopolymer only shows antimicrobial activity in acid media and, in this condition, achieves its highest solubility (2).

Chitosan offers distinct advantages that provide safe degradation products with no inflammatory effects; therefore, its exceptional properties, such as polycationic, non-toxic biocompatibility, biodegradability, bioadhesivity, antigenic capacity, antitumor, bioresorbable, and hemostasis (27,28), have led to its broad spectrum of biomedical applications in the pharmaceutical industry, especially in the elaboration of controlled release of drugs/enzymes/vaccine, tissue engineering, wound healing, blood anticoagulant, bone regeneration, as well as biosensing/bio-membrane manufacturing among others (29). Since the 1980s, chitosan and its derivatives have been used in Japanese products for the management of skin wounds (30).

Chemical properties of chitosan can be highly variable, depending on the source of obtaining, the method of deacetylation of chitin, molecular weight, viscosity, among others, and in turn impact on the functional properties of chitosan so that they can be manipulated according to its purpose. However, in the management of burn wounds, chitosan has been shown to have little or poor mechanical and handling properties. This is an important factor because the healing material that is used to counteract the loss of moisture by burning must be able to handle, provide moisture, absorb exudates, and promote healing.

For this reason, research has focused on finding coadjuvants that are compatible with chitosan to support its weaknesses and that can maximize or enhance the skin restoration effect (31,32). New formulations have been reported to adapt these biocomposites to the needs of the injury. Some studies like Alizadeh et al. (33) studied the interaction of gelatin–chitosan for the formulation of sponges as hemostatic agents. Wang et al. (34) studied hydrogel sheets based on chitosan with honey and gelatin as a cover for burn wounds. Zamora-Mora et al. (35) reported the preparation of chitosan–agarose hydrogels for their application in tissue engineering. Kang et al. (36) developed chitosan biocomposites treated with sodium hydroxide and sodium tripolyphosphate for hemostatic use. Ong et al. (37) prepared biocomposites based on chitosan incorporating polyphosphate as a pre-coagulant and silver as antimicrobial, both to accelerate blood coagulation, platelet adhesion, and absorb significantly more blood than pure chitosan composites. Nanomaterials based on chitosan show physical and chemical properties superior to those of pure chitosan. These new materials have a large surface area, have porosity, and have better resistance to deformation (38). Another advantage of chitosan in the treatment of burns is its ability to permeate oxygen for all tissues (39).

The molecular weight of chitosan is probably the most important property. Researchers have determined that using low molecular weight chitosan, even chitosan oligomers and monomers accelerate wound healing (40). Chitosan materials have been used to evaluate the acceleration of wound healing, and have been applied in different shapes such as powders, sponges, and granules. However, at the same time, cotton or polyester composites are used, and therefore the contact area between chitosan and injury site is too low to be able to estimate the effect of chitosan in accelerating wound healing.

2.2 Healing ability

Wound healing is a specific biological process related to the phenomenon of tissue growth and regeneration. Healing depends on several factors, including the person's medical condition, and the process progresses through a series of interdependent and overlapping stages, which involve biochemical complex and cellular processes. These stages include hemostasis, inflammation, proliferation, and remodeling (41).

In several studies, it has been reported that the use of chitosan accelerates the healing process and benefits each stage involved in the healing process. The hemostatic

properties of chitosan are directly due to the electrostatic interactions between the negative charges of the erythrocyte cell membrane and the positively charged chitosan (42). Clinically, when the chitosan materials are in contact with a wound, they adhere to cover the site of the injury by attracting red blood cells, forming a seal that prevents future hemorrhages (2).

In addition, chitosan is a promoter of tissue granulation by increasing the expression of collagen, among other components of the extracellular matrix, and accelerating wound healing (32). It also acts to improve the functions of proliferation and migration of inflammatory cells such as polymorphonuclear leukocytes, macrophages, and fibroblasts at the site of injury (Figure 2) (43).

Chitosan's biodegradable effect is attributed to lysozyme, an enzyme that is found in the human body and in various plants (25,38). It is known as a glycoside hydrolase that possesses the ability to slowly hydrolyze β -(1–4) bonds between *N*-acetylmuramic acid and *N*-acetyl-D-glucosamine residues or between *N*-acetyl-D-glucosamine residues of chitosan membranes (2). The degradation by lysozyme allows the reabsorption of the coating and the release of *N*-acetyl glucosamine among other oligomers, which activate the macrophages and are incorporated into the extracellular matrix for the reconstruction of normal physiological tissues (44).

2.3 Antimicrobial activity

An antimicrobial is an agent that eliminates microorganisms or inhibits their growth (25). Despite great progress in the management of burn scars, infections are the greatest challenge causing morbidity and mortality. *Candida* spp. it is one of the microorganisms that often colonize burn scars causing persistent infections, loss of skin graft, and delaying the healing process (45).

For an antimicrobial polymer to be ideal, it must be economically synthesized, stable in the long term, soluble in water or neutral medium, must not be decomposed into toxic products or emit them, and must have bactericidal activity against pathogens in short contact times (46). Chitosan has been shown to have advantages over other antimicrobials because it has a high antimicrobial activity, a broad spectrum of activity, and a higher mortality rate (47).

Chitosan is a potent antimicrobial agent of cationic nature at a pH lower than 6.3 (48). Hypotheses indicate that chitosan could interact with anionic groups on the cell surface of microorganisms increasing the permeability of membranes, facilitating the leakage of proteins

Figure 2: Graphic representation of the application of chitosan in wound healing.

and other intracellular constituents of microorganisms (43). Another mechanism involves the formation of chitosan chelates with trace elements or nutrients resulting in the inhibition of enzymatic activity (49) due to the chitosan–DNA interaction that alters the synthesis of messenger RNA (50). The antimicrobial effects are regulated by intrinsic factors that include the type of chitosan, the degree of polymerization of the chitosan, the source, and the chemical composition of the substrates.

Malinowska-Panczyk *et al.* (51) studied the antimicrobial properties of chitosan films of different degrees of deacetylation (DD) and molecular weight against Gram-positive and Gram-negative bacteria. With this, they demonstrated that the stage of inactivation of the bacteria increases with the increase in the DD of the biopolymer; however, the mechanism of bacteriostatic and bactericidal actions is not fully known.

Some studies on animals have been carried out using chitosan, proving that this product is superior to others in the elimination of infection and in the promotion of new tissue. However, few clinical cases have been used chitosan in the treatment of skin lesions such as ulcers (52).

The chitosan–gelatin composites prepared by Pereda *et al.* (53) have a inhibitory activity against Gram-positive and Gram-negative microorganisms. Ahmed and Ikram (25) reported that the biocomposites with more than 0.025% chitosan inhibit the growth of *Escherichia coli*, *Fusarium*, *Alternaria*, and *Helminthosporium*. Wang *et al.* (34) evaluated the antimicrobial activity of chitosan, honey, and gelatin hydrogels as possible coatings for the healing of

burn wounds and reported that the hydrogels have an action against *Staphylococcus aureus* and *E. coli*. Liu *et al.* (48) added polyvinyl alcohol (PVA) to chitosan solutions for the production of nanofibers with multiple applications and reported bacteriostatic activity against *E. coli*. According to research conducted by Anisha *et al.* (54), the application of chitosan sponges for the treatment of diabetic foot ulcers prevents polymicrobial infection and decreases the risk of amputation.

3 *In vitro* studies

The safety and effectiveness of medical devices made of resorbable biomaterials depend to a large extent on their complete biocompatibility (55). That is, the tissues and the human body fully accept the implantable material and do not cause a massive immune response as a result of a threatening material.

Hemocompatibility studies have established that the lower the value of the hemolysis ratio, the better the compatibility of the biomaterial with the blood. Some authors have reported that a value of up to 5% hemolysis is permissible for biomaterials. *In vitro* studies with nanomaterials based on chitosan, hemolysis values of 1.14% have been reported, this after 60 min of contact of the material with the blood (56).

Chen *et al.* (57) investigated the hemostatic mechanism of biomaterials, through the reaction with erythrocytes,

comparing conventional medical gauzes, polyurethane sponges, absorbent dressings of chitosan, and the aqueous solution of chitosan. In these experimental studies, changes were observed in the shape of the erythrocytes on contact with conventional gauze and polyurethane sponges, attributed to the morphological changes of the red blood cells by external stimuli and no aggregation was observed. While in the porous sponges of chitosan, the erythrocytes showed deformation and their incorporation on the surface of the sponges, as a result of a hemostatic reaction. The agglutination of blood cells by the action of chitosan can be the result of the interaction of the positive charges of the polymer with the receptors on the cell surface of erythrocytes.

Alizadeh et al. (33) investigated the *in vitro* biodegradation of chitosan–gelatin dressings with lysozyme and observed that the destruction of the structure was 28% at day 8 at 37°C. Additionally, Arpornmaeklong et al. (58) evaluated enzyme activity in lyophilized hydrogels of chitosan–collagen. These dressings exhibited a dynamic degradation from day 14. This was attributed to the hydrophobicity of the sponges that causes the biodegradation and excision of the bonds after the swelling of the matrix.

The epidermal growth factor (EGF) is a mitogenic peptide, involved in the regulation of physiological processes such as growth, cell proliferation, regeneration, and wound repair. It also stimulates messenger RNA, DNA, and protein synthesis in many cell types and has been shown to stimulate keratinocyte division *in vitro* and epidermal regeneration *in vivo* (59).

Ceren et al. (60) determined the *in vitro* release of EGF from the chitosan gel formulation to be 97.3% at a pH of 5.8 in a period of 24 h. However, the release kinetics was of first order. This result indicates that the rate of EGF release from the gel is variable with time.

Yenilmez et al. (59) evaluated the stability of chitosan by changes in pH for 6 months. It was determined that the chitosan solution of lower concentration remained unchanged in its pH. Later, egg yolk oil and EGF were added to the stable formulation for future *in vivo* studies.

Because of low molecular weight chitosan, even chitosan oligomers and monomers accelerate wound healing and have better antimicrobial properties. Recent research studies new formulations mixing chitosan with curcumin nanoparticles and using microwave technology to reduce molecular weight and increase the DD. Curcumin is a drug with powerful antioxidant and antibacterial attributes that promote tissue regeneration. Hafiz et al. (61) determined that chitosan of low molecular weight, low viscosity, smaller particle size, and higher surface charge helps to produce smaller nanoparticles with a more efficient

penetration at the site of the injury and therefore releases the drug more effectively.

Other investigations on the incorporation of antibiotic nanoparticles, such as gentamicin to chitosan, showed that the release of the drug is controlled by the diffusion and degradation of the polymeric matrix (62).

4 Studies in animal models

Burns can be classified according to their degree of severity as wounds with loss of tissue and wounds without loss of tissue. For this cause, few studies have reported the effectiveness of chitosan alone, as an antimicrobial and healing agent in its different forms. Bayat et al. (20) performed the application of 2% (w/v) chitosan nanofibers on second-degree burns in rats. The nanofibers were changed every 2 days, and biopsies were taken within 21 days. On day 7, granulation tissue formation was observed, including fibroblast proliferation and angiogenesis. The results showed almost complete regeneration of skin and hair at 21 days.

Nacer Khodja et al. (63) evaluated the healing activity of chitosan coatings in second-degree burns in rats. The coatings were replaced every 2 days in the inflammatory phase, every 3–4 days in the proliferative phase, and every 4–7 days during the maturation phase. The authors observed that 90% of the healing of the burn was achieved between days 9 and 12. Similar results were reported by Sung et al. (64) when applying chitosan dressings loaded with antibiotics, observing that the size of the induced wound decreases approximately 90% at day 15.

To assess the healing efficiency in female pigs, chitosan hydrogel was applied as a coating in third-degree burns, and the dermal–epidermal reconstruction and re-epithelialization of the affected area were observed without irritations or harmful effects. After 10 months of skin involvement, it was observed that the quality of healing, in terms of thickness, was better with chitosan hydrogels than with commercial gauze (65).

Honardar et al. (66) studied the speed and effectiveness of the healing of second-degree burns in rabbits by applying chitosan gel. They confirmed the acceleration of healing microscopically on the 20th day, as a consequence of the proliferation of epidermal cells with complete epithelialization of the affected area.

Histological observations of the effect of local application of chitosan and heparin on partial depth burns in adult rats indicate that burns are less severe than control wounds (67). This is because the mixture of chitosan and heparin inhibits the inflammatory reaction.

Table 1: Summary of *in vivo* studies and main findings

Year	Characteristics of chitosan	Chitosan blend	Animal model	Main results	References
2021	ND	Carboxymethyl chitosan, hyaluronic acid, and silver	Burns on rats	Significative wound contraction, granulation tissue formation, inflammatory infiltration, and collagen fibers deposit	(69)
2019	DD 98%, MW 15 kDa	Glycerol-plasticized chitosan and PVA membranes	Burns on rabbits	Phase of peripheral inflammation in 3 days. Significant healing effect over a period of 15 days	(12)
2019	Low molecular weight chitosan	Chitosan and bromelain nanofibers	Burns on rats	Granulation tissue on day 7. Complete regeneration of skin and hair on day 21	(20)
2016	ND	Chitosan-based topical gel	Burns on rabbits	Acceleration of healing microscopically on day 20	(66)
2015	Highly viscous	Chitosan, egg yolk oil, and EGF	Burns on rats	Dramatic changes in wound contraction on day 21 day	(59)
2014	Low molecular weight chitosan	<i>Aloe vera</i> , chitosan, and vitamin E	Burns on rats	The material has mucoadhesive properties influenced by chitosan. Re-epithelialization after 14 days	(68)
2013	DD 70%, MW 471 kDa	Chitosan and PVA	Burns on rats	90% of the healing was achieved between days 9 and 12	(63)
2011	ND	Sodium alginate and chitosan films	Burns on rats	Low level laser therapy with chitosan and alginate improves epithelialization and vascularization	(31)
2010	DD >75%, viscosity 800–2,000 cps	Minocycline-loaded dressings with PVA and chitosan	Burns on rats	Wound decreases approximately 90% on day 15	(64)
2007	DA 2.6%, MW 540,000 g·mol ⁻¹	Chitosan hydrogels	Wounds on female pigs backs	Quality of healing in terms of thickness was better with chitosan hydrogels than with commercial gauze	(65)
2007	DD >90%, MW 500,000 g·mol ⁻¹	Chitosan and heparin	Burns on rats	Mixture of chitosan and heparin inhibit the inflammatory reaction	(67)
2006	MW 650,000 g·mol ⁻¹ , viscosity 7,903 mPa at 25°C	Chitosan with EGF	Burns on rats	Treatment with EGF and chitosan gel decreased the wound healing period	(60)

DA, degree of acetylation; DD, degree of deacetylation; MW, molecular weight; and ND, not determined.

Pereira et al. (68) developed a gel of microparticles based on chitosan added with *Aloe vera* and vitamin E for the treatment of burns. This material has mucoadhesive properties influenced by chitosan, which favored re-epithelialization after 14 days of treatment in mice.

Dantas et al. (31) proposed to combine sodium alginate with chitosan for the production of films with the aim of improving cutaneous healing by burns in rats. They concluded that the combination of low-level laser therapy with chitosan and alginate-based films improves healing, specifically with respect to epithelialization and vascularization.

Wang et al. (34) used chitosan hydrogels with gelatin and honey as coatings for second-degree burns in rabbits. The mixture of chitosan and honey showed a positive synergism in terms of antibacterial activity. This fulfills the primary objective of the treatment of burns, which implies preventing infection and acting as an effective promoter of healing.

Bano et al. (12) analyzed second-degree burns on rabbits, using chitosan-PVA membranes, and observed initial phases of peripheral inflammation in the first 3 days of experimentation; chitosan membranes showed a significant healing effect over a period of 15 days.

Ceren et al. (60) determined that the efficient release of growth factors that accelerate burn healing should be considered. Chitosan was proposed as a polymer for controlled release. The results were evaluated immunohistochemically on the 7th day of therapy; the maximum cell proliferation was found in the application of the gel formulation with EGF.

Yenilmez et al. (59) measured burn wound healing contraction over a 21 day period. The researchers used the mixture of chitosan-egg yolk oil and EGF. The formulation showed significant shrinkage compared to commercial Silverdin[®] products and control groups (no treatment). The most dramatic changes were evidenced on day 21, epithelialization was mostly completed, and even the formation of a new vein and collagen fibers between layers was detected. Table 1 summarizes the main results reported in the *in vivo* studies.

5 Clinical cases

The data on the toxicity of chitosan in human studies are very limited. Hamed et al. (70) summarize trials conducted in humans in recent years. It was reported that quantities above 4.5 g of chitosan taken daily did not cause toxic effects, and other clinical trials performed

for more than 12 weeks, showed no significant clinical symptoms and no allergic response.

Escárcega-Galaz et al. (52) reported a clinical case where eight patients received treatment in wounds and ulcerative lesions associated with diabetes mellitus located in the lower limbs, reported that at the end of the treatment period only one of the patients experienced complete recovery, while the other patients experienced significant progress in their injuries.

Carles et al. (71) presented four cases of the use of a commercial product of chitosan (Celox[®]) to stop potentially fatal obstetric hemorrhage for the patient: two cases applied gauzes with chitosan and two applied the chitosan powder product, and the results indicated that the chitosan quickly stopped the bleeding, constituting a new economic alternative and that may be available in developing countries.

Some chitosan products available on the market are used for hemostatic use, among which are HemCon Dental Dressing (HemCon Medical Technologies, Inc, Beaverton, OR), ChitoSAM[™] 100 is a 100% chitosan dressing, Celox[™] (72) sells chitosan products (OMNI-STAT[™]) for topical application in hospital procedures and in the emergency room, the clinical trials performed showed significant time reduction to achieve hemostasis. AxioStat[®], -brand has products based on clinically validated patents of Axio clotting technology, recommended to stop arterial hemorrhages and during vascular procedures.

Those individuals who have suffered from severe skin loss from burns are at higher risk of dying from fluid loss, as well as massive infections. The application of chitosan biomaterials for the healing of various burns has been reported in recent clinical studies. Table 2 describes the clinical trials where chitosan-based dressings were applied as a coating for wounds. In all cases, uniform adherence to the wound is reported, which is a requirement for a successful biomaterial. Another requirement is the promotion of hemostasis, healing, and rapid re-epithelialization of the affected area, transforming it into new healthy and aesthetically acceptable tissue.

6 Conclusions

Burn trauma is one of the most difficult challenges that patients can present; as a consequence, it is common to observe infections, wounds, scars, and psychological damage. In this review, it has been highlighted recent research that shows the biological and antimicrobial properties of chitosan favor the restoration of cutaneous

Table 2: Summary of clinical trials using chitosan in the treatment of chronic wounds

Year	Coatings	No. of patients	Wound type	Main results	References
2020	Topical gel containing chitosan	36	Incision for lower third molar tooth extraction	<ul style="list-style-type: none"> • 2 days after surgical removal, patients evaluated wound healing on a scale of good, acceptable, and bad • Chitosan gel was considered good in 41.7 and 0% on the placebo treatment 	(73)
2020	Chitosan-based chewing gum	36	Reduction of salivary <i>Streptococcus mutans</i> counts	<ul style="list-style-type: none"> • Chitosan chewing gum has a positive effect on the reduction of numbers of salivary <i>S. mutans</i> colonies 	(74)
2019	Chitosan dressings	10	Cutaneous lesions	<ul style="list-style-type: none"> • Patients showed significant (30%) or complete (70%) improvement after 8 weeks of therapy. At 16 weeks posttreatment, all cases were completely cured • It was well tolerated, and there were no product-related adverse events such as allergic reaction or infection 	(75)
2019	Chitosan brush	11	Dental implants with peri-implant mucositis	<ul style="list-style-type: none"> • Implants treated with the chitosan brush had a better improvement in bleeding on probing at 2 and 4 weeks compared with titanium curettes 	(76)
2018	Chitosan dressings	277	Lower third molar extraction	<ul style="list-style-type: none"> • Better radiographic findings at second week. Improved bone formation 	(43)
2018	Chitosan films	244	Superficial wounds	<ul style="list-style-type: none"> • Showed less exudate and less odor • Ease removal, no edema, or localized warmth was observed • No infection 	(77)
2017	Chitosan dressings with silver	10	Partial thickness pediatric burns	<ul style="list-style-type: none"> • Full healing in 8.3 days • The coating forms a gel to moisten with saline maintaining its original size • The lack of contraction of the coating provides a high degree of patient comfort 	(42)
2008	Chitosan films with oleic acid	2	Tissue donor area burn type AB/B	<ul style="list-style-type: none"> • Complete epithelialization on day 12 • Complete epithelialization at day 15, with good appearance and functionality of the scar • Uniform adhesion of the film to the wound 	(39)
2004	Chitosan films	20	Tissue donor area	<ul style="list-style-type: none"> • Healthy, clean, and bright pink area on the 10th day • Pain assessment less than 2 • Abundant formation of inflammatory cells, fibroblasts, and keratinocytes 	(30)
2000	Chitosan dressings	20	Tissue donor area	<ul style="list-style-type: none"> • Re-epithelialization faster than the control areas • Healing in 10.4 days • Biopsies showed small nerve fibers and flexible connective tissue in the papillary dermis 	(78)
1991	Carboxymethyl chitosan dressings	4	Tissue donor area	<ul style="list-style-type: none"> • Better histological order and vascularization • Absence of inflammatory cells 	(79)

tissues and benefit human health. In addition, clinical trials are shown regarding the treatment of burns and donor areas with films or coatings based on chitosan. Although there are few clinical cases reported to date on the application of chitosan in burns, the results have indicated that the therapeutic application of chitosan is effective for skin regeneration, constituting an effective alternative treatment especially in developing countries.

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