Alternative Treatment of Bacterial Wound Infections

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Alternative Treatment

Topical and systemic antibiotic treatment are essential in the prevention and treatment of wound infections. Systemic antibiotics, on the other hand, are strongly linked to mechanisms of resistance, which jeopardize the treatment process. The direction of systemic antibiotics to the eschar becomes less reliable the deeper the burn and the thicker the eschar becomes for local wound care (Noronha and Almeida, 2000). As a result, topical antibiotics appear as a viable treatment option, as they help to maintain a "high and sustained concentration of the antimicrobial at the infection site" (Cowling and Jones, 2017).

Every year, wound treatment develops a high urgent clinical problem, as The requirement for wound care has an influence on a significant percentage of the global population. The system of healthcare in the United States spends $20 million a year on wounds (Jackson, 2006). An Incisional, acute, and chronic wounds are all examples of wounds that can become infected and lead to more complications.

Incisional wounds and deep lacerations are often troublesome, and they account for a significant portion of the annual cost of wound healing products. While Wounds from incisions heal more quickly than chronic wounds, they always have challenges with appropriate closure as well as the formation of granulation tissue, which might lower one's quality of life. Wounds from incisions are also susceptible to infection, necessitating further care. Antiseptics, antibiotics, as well as silver dressings have traditionally is always used to treat wounds, however each of these therapies is ineffective against a wide range of microorganisms often present in wounds.

However, if no appropriate clinical intervention is used, skin regeneration and overall healing time would be significantly slowed. While It's possible to use recombinant growth factors and tissue-engineered wound dressings, they are extremely costly and out of reach for the majority of illnesses (Shevchenko *et al*., 2010). In extreme burns, (SSD) silver sulfadiazine is the preferred transdermal substance, and it is almost universally used today over silver nitrate as well as mafenide acetate. Although SSD cream works excellent., it can effect recurrent side effects such as erythema multiforme, neutropenia, methemoglobinemia, and crystalluria (Hosnuter *et al*., 2004). As a result of this restriction, there has been an increase in interest in the development of a suitable biological wound care dressing that can provide the appropriate milieu for wound healing as well as protection during the process of healing.

It possesses antifungal, antimicrobial, additionally antibacterial characteristics, which are particularly effective in wound care. It also increases the host's defenses to avoid infection. (Azuma et *al.*, 2015). Several research groups around the world are

looking into chitosan as a potential wound healing material because it has unique homeostatic, granulation, and epithelization properties (Tang *et al*., 2016).

Dressings for Wounds

Thousands of patients are harmed or burned each year as a result of hot water, fires, injuries, or boiling oil. These accidents can potentially leave you permanently disabled. high-cost care, or even death. More than 30,000 people die each year from scalds and burns, according to the World Health Organization **(**Kamoun *et al*., 2015). Both individuals are people over the age of 65, and they are dealing with issues where skin regeneration will never occur on its own. Because auto skin healing is so common, bruising is commonly associated with it. With time, for skin tissue repair or healing, polymeric dressing materials become unavoidable due to the conventional approach's inability to meet the criteria for significant loss of dermis (Figure 1) (Fansler *et al*., 1995).

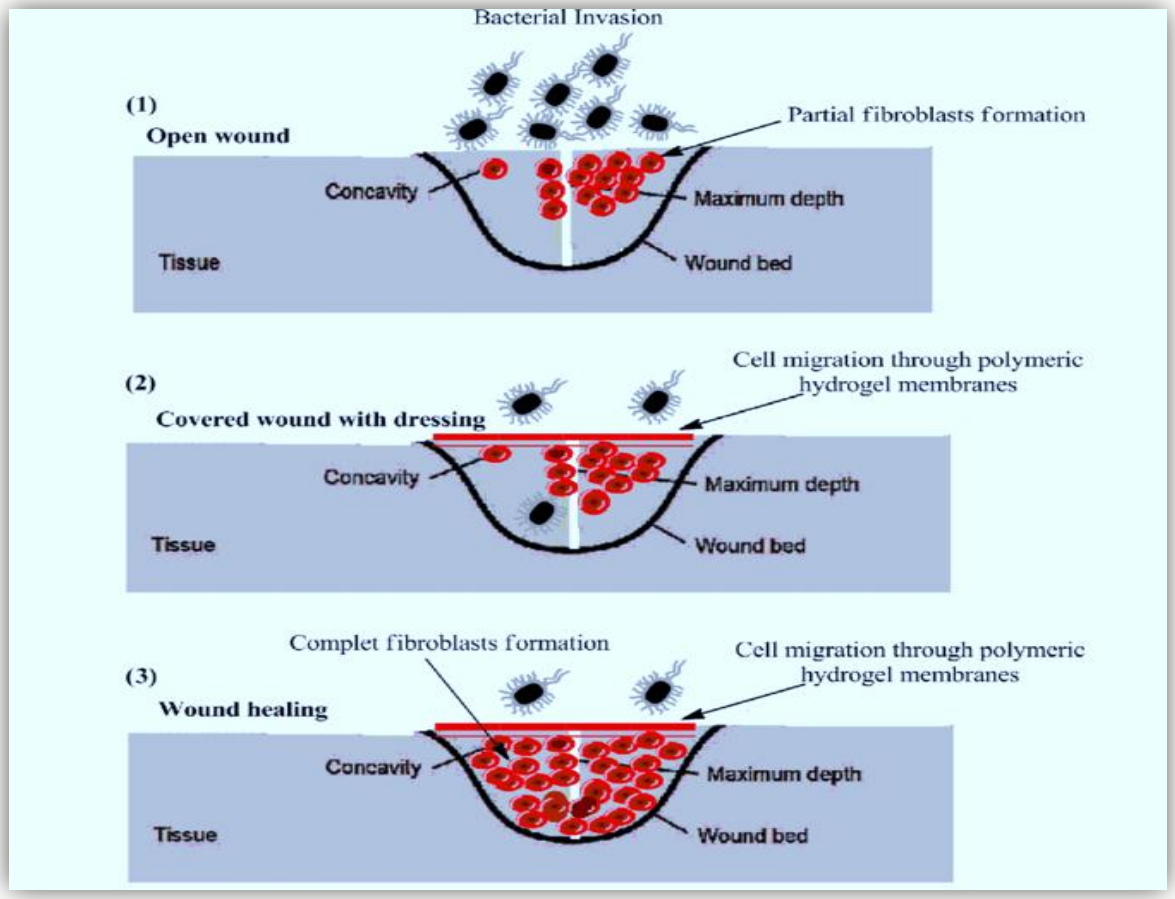

Figure (1): Representation of the role of hydrogel membrane materials for enhancing and accelerating the wound healing phases (Fansler *et al*., 1995).

Every silver dressing on the market has its own set of benefits and drawbacks. While most current models destroy or the growth of a variety of wound infections is inhibited, though they have a number of flaws that can be fixed and improved. According to one report, many of the dressings contain more than five times the amount of silver needed to kill most microbes (Demling, 2002).

Gary Ostroff has undertaken significant research on these chemicals utilizing thirty-two formulations (Ostroff, 2005). By measuring the different terpenes against ten wound pathogens, their potent antibacterial activities were discovered by Ostroff and coworkers. Many terpenes were found to have broad antibacterial activity against bacteria such as *Staphylococcus aureus*, *Streptococcus pyogenes*, and *Candida albicans*. Terpenes, on the other hand, were ineffective against wound pathogens like *P. aeruginosa*. Silver, on the other hand, has been shown to be very effective against these bacteria in studies (Ostroff, 2005). As a result, combining silver and terpenes in a dressing to inhibit a wider range of wound pathogens may be a promising option for developing the next generation of wound care plasters (Wright, 2002).

Terpenes are not only antibacterial, but they are also less expensive than silver due to their organic origin. Many of these substances have a pleasant odor (Ostroff, 2005).

Any implant or wound dressing must be able to attract the right cells or receptors to the skin's surface. These cells and receptors are critical because they are responsible for initiating and supporting certain responses, such as blood clotting and macrophage start. The dressing will prevent tissue regeneration and repair if it lacks the required cellular components and receptors (Ratner, 2004). For a skin graft, keratinocytes are seeded into a synthetic collagen matrix, because keratinocytes are a normal part of the body and promote favorable biological functions for the collagen, they assist the graft be tolerated by the body more readily (Harrison *et al*., 2006). The graft may be rejected by the body without the keratinocyte cells on the surface, and healing and regeneration of new tissue will take longer.

Chitosan and Nano Chitosan

Chitosan is a natural unbranched homopolymer created by eliminating the acetyl groups COCH3 from the chitin original structure with alkali (Figure 2). (Kurita, 2006). Chitosan is a cationic natural polysaccharide made from glucosamine and N-acetyl glucosamine and produced by deacetylating chitin. Chitosan is a nontoxic, biodegradable, and biocompatible chemical that is employed in a variety of biopharmaceutical studies (Cheung et al., 2015). It works as a wound healer by enhancing the natural production of hyaluronic acid at the wound site. It also accelerates wound healing and nerve regeneration in the vascular dermis (Jayakumar et al., 2011).

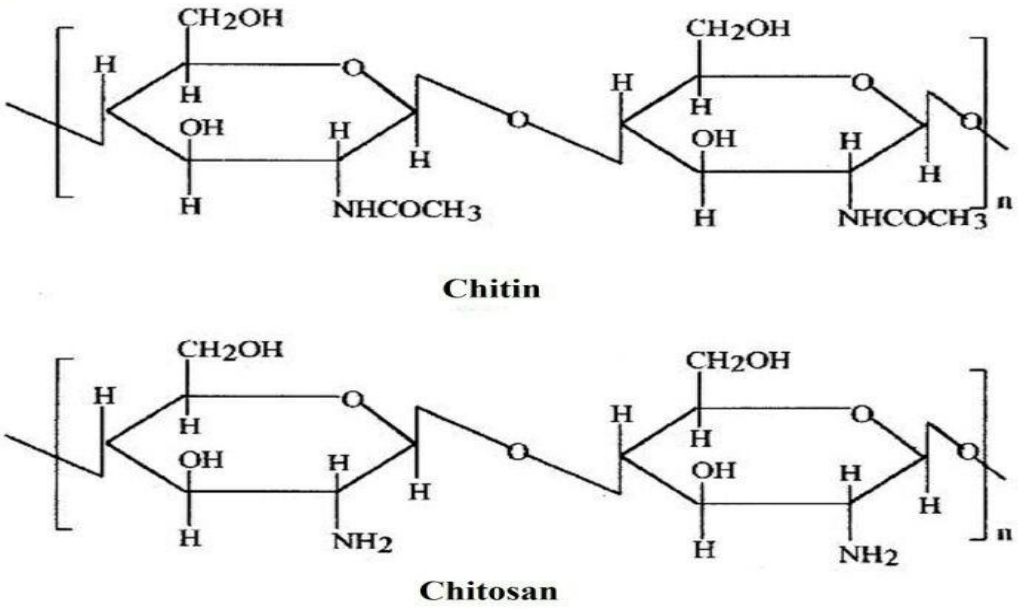

Figure (2): Chemical structure for chitin and chitosan (Naira and Laurencin, 2007).

Chitosan is a non-toxic polymer with a large molecular mass that looks like cellulose, a plant fiber. The main difference between chitosan and cellulose is that in position C-2, chitosan has an amine (-NH2) group instead of cellulose's hydroxyl group (-OH). Chitosan, unlike plant fiber, possesses positive ionic charges that enable it to chemically bond to negatively charged fats, lipids, cholesterol, metal ions, proteins, and macromolecules (Li et al., 1992).

Chitosan is a chitin derivative, which can be found in the shells of lobster, crab, as well as shrimp. It can also available in everyday foods like barley, yeast, bananas, and mushrooms. Deproteinized, demineralized, and deacetylated chitin. It's a fiber of dietary, which means it can't be broken down by a person's digestive enzymes (Razdan and Pettersson, 1994). In this respect (Rout, 2001), due to their excellent properties, Biocompatibility, biodegradability, adsorption, the ability to build films, and the capability to chelate metal ions have all sparked increased commercial interest in chitin and chitosan as possible resource materials.

Nano-chitosan is a natural substance of outstanding physical and chemical properties. It is bioactive and environmentally friendly. Physical interlocking by ionic gelation between chitosan and unique negatively charged macromolecules like pent sodium tripolyphosphate has been used to make nano-chitosan (Calvo *et al*., 1997).

Furthermore, chitosan and chitosan nanoparticle films and coatings can be employed as a carrier for natural or artificial antibacterial agents, antioxidants, enzymes, or functional compounds like plant extracts, probiotics, minerals, or vitamins (Ojagh *et al*., 2010).

Many researchers regarding this point have highlighted chitosan and its derivatives' antibacterial action modes: (i) Chitosan acts as a chelating agent, which is one of the mechanisms (Rabea *et al*., 2003).

(ii)After that, it interacts with DNA and interferes with protein mRNA synthesis, inhibiting the action of various enzymes.

(iii) The third point made by Chung *et al*., (2004) suggests that when chitosan interacts with negatively charged cell surfaces, it causes more changes in cell wall structure and cell membrane permeability. As a result, it will have a major impact on Gram-negative bacteria.

Each monomer of the final chitosan structure has one primary amine and two free hydroxyl groups, as well as the structural formula is $C_6H_{11}O_4N$. Chitosan has a high film-forming capacity and has been widely tested for food preservation applications due to its versatility (Britto and Assis, 2007). It was employed in biological applications by (Singh and Ray 2000), as a material for chemical encapsulation and controlled release additionally for environmental cleanup by Patel and Jivani 2009). (Assis and Britto, 2008), as well as for environmental remediation (Assis and Britto, 2008). Chitosan is obtained commercially from a different sources, including lobster, shrimp, crabs, and so on, and is typically sold in flakes form or powder. The key parameters that determine the solubility as well physic-chemical properties of this polymer are its degree of deacetylation and molecular weight. Chitosan must first be dissolved into gel by sufficient dissolution of solvent before being converted into films or parts. Crude chitosan, on the other hand, is only soluble in an acidic environment with a pH under its pKa (around 6.4). This is a disadvantage for chitosan's wider applications, because pH affects its biocompatibility and properties of film mechanical (Kurita, 2006). (Britto *et al*., 2005). If molecules of chitosan are subjected to the intense methylation process, the amino groups of quaternization produces a trimethyl chitosan (TMC) is a derivative salt having permanent positive charges (Britto and Assis, 2007b). Chitosan possesses a cationic characteristic that is independent of the pH of the solvent due to these charges in the polymer backbone. TMC can be turned into a gel in a neutral medium, making it more suited for use in food and medicine (Ji et al., 2009).

The fundamental antibacterial mechanism is anticipated to be the electrostatic interaction between positively charged R N(CH3)3+sites and negatively charged microbial cell membranes, which is predicted to be important for cellular lysis (Rabea et al., 2003 ; Tripathi et al., 2008). By combining with vital nutrients, charged chitosan can inhibit bacteria development (Jia et al., 2001).

Characterization of Chitosan

Chitosan's antibacterial capabilities versus a wide microorganisms spectrum have been examined. Chitosan's antibacterial action is influenced by both its molecular weight and degree of acetylation **(**Mellegard *et al*., 2011; Hosseinnejad and Jafari, 2016), in comparison to the degree of acetylation, the molecular weight has a greater impact on antibacterial action **(**Goy *et al*., 2009 ; Younes *et al*., 2014). Antimicrobial action has been observed to increase with increasing molecular weight in acid (Li et al., 2016). At pH 7.0, the antibacterial activity changed (Chang et al., 2015).

Antimicrobial Mechanisms of Chitosan

Overuse of antibiotics has resulted in antibiotic resistance, which has become a major as well as increase issue around the world. According to the World Health Organization (WHO) as well as the Centers for Disease Prevention and Control

(CDC), superbugs such as methicillin-resistant S. aureus (MRSA), multiple-drug resistant (MDR) Enterobacteriaceae, Acinetobacter, and Pseudomonas, and serious drug-resistant Mycobacterium tuberculosis have become the most prevalent pathogens causes of mortality in recent decades (Watkins and Bonomo, 2016). Chitosan is a polysaccharide made up N-acetyl glucosamine units and glucosamine found in nature. However, Antimicrobial activities of chitosan are influenced by molecular weight, deacetylation level, and positive charge content (Chang, et al., 2015). To enhance antimicrobial activity, some studies have added sulfonate or quaternary ammonium groups to chitosan, as well as antibacterial herbs or enzymes to chitosan-based beads or nanoparticles (Sahariah *et al*., 2015 ; Wu *et al*., 2017).

(1) Chitosan has outstanding inhibitory effect against a wide range of microorganisms, including fungus, trypanosomes, and bacteria, thanks to its cationic characteristics (Wang et al., 2015).

(2) Negatively charged microbial cell membranes can interact with positively charged chitosan molecules, resulting in changes in cell wall permeability and the leakage of internal chemicals (Chang et al., 2015).

One of chitosan's widely investigated features is its antibacterial activity, which has uses in biomedicine, cosmetics, food, and agriculture. To date, several research have been carried out in attempt to use chitosan's antibacterial activity as well as its unique features to build self-preserving substances. As a result, a broad range of chitosan-based products, such as beads, films, fibers, membranes, and hydrogels, have been developed for a variety of applications (Perinelli et al., 2018).

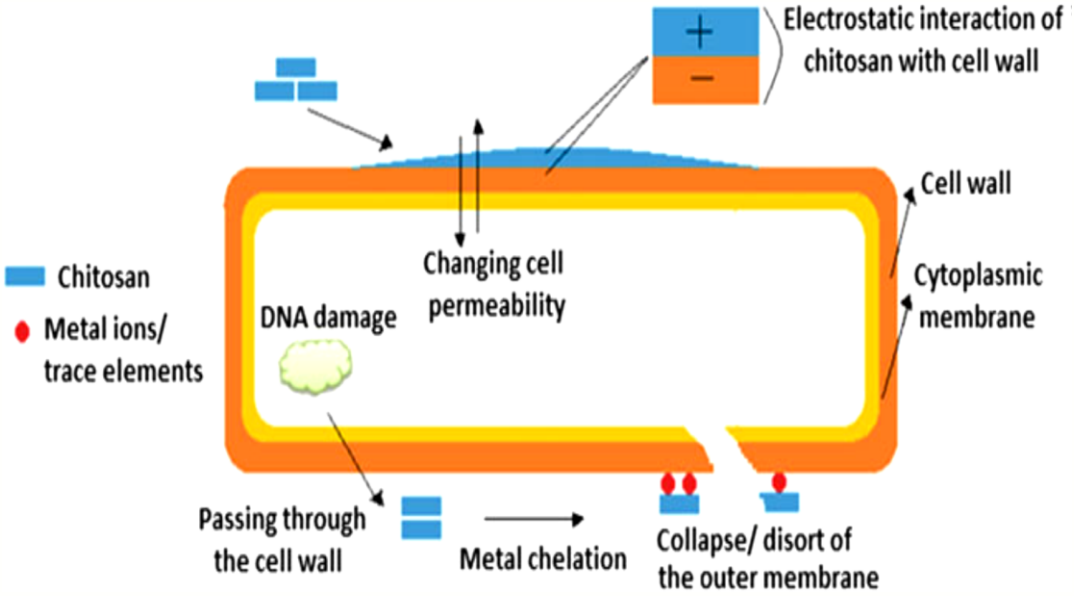

Figure (3): Antimicrobial mechanisms of chitosan and its derivatives are depicted in a diagram (Hosseinnejad and Jafari ; 2016).

Chitosan has been extensively used as a carrier material in drug delivery applications. Chitosan's cationic character, which is based on its main amino groups, gives the polymer distinct biophysical and biochemical capabilities. Chitosan nanoparticles provide unique advantages over other forms of delivery methods, such as gradual and controlled drug release, higher drug absorption and improved bioavailability, less

pharmacological side effects, and so on (Elgadir et al., 2015). Nano medicine refers to the use of nanotechnology in the treatment, diagnosis, monitoring, and control of diseases. Drug delivery and cancer therapy are two of the most useful applications of nanoparticles in medicine (Drbohlavova et al., 2013). Chitosan can be used to administer medications by oral, ophthalmic, nasal, vaginal, buccal, parenteral, and intravesical routes, among others (Bernkop-Schnürch and Dünnhaupt, 2012).

Investigations on chitosan modification are expanding in biomedical and pharmaceutical applications to increase its already established antibacterial capabilities against Staphylococcus aureus and Escherichia coli. Because the biopolymer's bactericidal efficacy has been already studied and validated, these bacteria are the most prevalent in the scientific context (Mahae et al., 2011). Chitosan is a potential material for a variety of uses, and chemical modifications could boost its inhibitory action on harmful microbes and help with the resistance problem (Chang et al., 2015). Chitosan has a well-studied biocompatibility profile, making it a suitable biopolymer for implantable devices and medication delivery (Raafat, and Sahl, 2009). Antibiotics and antimicrobials can be combined directly into viscous chitosan solutions, which can then be utilized to manufacture films, beads, and other drug delivery systems (Landriscina et al., 2015). Vancomycin is a glycopeptide antibiotic commonly used parenterally for the treatment of infected wounds in hospitalized patients due to its broad spectrum of activity against Gram-positive bacteria, and is especially indicated when methicillin-resistant S. aureus infection is suspected (Kosinski and Lipsky, 2010). The amino groups in deacetylated chitosan provide functional points of attachment for pharmaceuticals or polymeric systems to react with, physically binding the drug to change the drug release profile (Park et al., 2010). Chitosan polymers' viscous nature makes them ideal for usage as a tablet binder and coating ingredient (Drechsler et al., 2014). Because of chitosan's biodegradability, drug delivery systems can eliminate surgical removal operations after the drug is given (Movaffagh et al., 2013). Because of its cationic charge and hydrogen bonding interactions, chitosan has the property of being mucoadhesive, attaching to mucin molecules in the mucous layer that covers epithelial tissues (Sogias et al., 2008). While a cell-based treatment is more probable to provide a true cure for diabetes than exogenous insulin, eliminating the need for daily insulin injections is still preferable. As a result, chitosan is being studied as part of an oral insulin delivery system. Due to the problems such as protein denaturation due to the high pH of the stomach, enzymatic breakdown due to digestion, and difficulties moving proteins across the intestinal wall, an oral replacement dependent only on insulin is not accessible (Song et al., 2014). Because of its cationic activity, chitosan improves adherence to the mucosal membrane and promotes the opening of tight junctions in the cell membrane, increasing mucosal absorption of small molecules, peptides, and proteins (Illum, 1998). In solution, chitosan creates insoluble compounds with negatively charged insulin; however, these complexes are unstable in the acidic stomach (Hamman, 2010). Song *et al*., (2014) nanocoated insulin–chitosan micro particles with seven alternating layers of chitosan and heparin previously.

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