A Review: Natural Polymer Based Hydrogel Wound Dressings in The Wound Healing of Diabetics' Patients

By

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A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (Hons.)

School Of Pharmacy
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Declaration

It is hereby declared that

1. The project submitted is my own original work while completing degree at Brac University.
2. The project does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The project does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

Student's Full Name & Signature:

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Approval

The thesis titled "Natural Polymer Based Hydrogel Wound Dressings in The Wound Healing of Diabetics' Patients" submitted by Manjila Saliha Proma, ID: 19146067 of Summer, 2022 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy.

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Ethics Statement

There were no tests on animals or humans as part of this project.

Abstract

Hydrogels are largely used as convenient dressing materials for promoting a moist and healing-friendly environment, particularly in the treatment of chronic wounds such as diabetic wounds. The properties of natural polymer-based hydrogels, extracted from sources such as plants, animals, and microorganisms, have a significant impact on wound recovery by absorbing exudate, promoting cell growth, altering tissue structure, and working as effective dressing materials. Some commonly used biopolymers include cellulose, chitosan, alginate, and hyaluronic acid. These hydrogels have favorable properties such as 3D polymeric networks, hydrophilicity, and absorption abilities for creating a moist and efficient healing environment. In the future, advancements in hydrogel technology, such as increasing mechanical stability, balancing molecular weight, and optimizing physiological processes in microorganisms, will improve the use of hydrogels in wound healing.

Keywords: Hydrogel; Chitosan; Cellulose; Alginate; Hyaluronic acid; Diabetic wound healing.

Dedication

This paper is dedicated to my outstanding supervisor, Tanisha Momtaz, Lecturer, School of Pharmacy, BRAC University, in acknowledgment of your valuable guidance and assistance throughout my academic journey as well as during this project at the School of Pharmacy. Your devotion to educating and mentoring has had a great impact on my development, and I am eternally thankful. I also dedicate this work to my family for their immense support in every thick and thin of my life.

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Table of Contents

List of Figures

List of Acronyms

IDF: International Diabetes Federation

3D: Three Dimensional

PEG: Polyethylene glycol

DDS: Drug Delivery System

ECM: Extracellular Matrix

BC: Bacterial Cellulose

PC: Plant Cellulose

CMC: Carboxymethyl Cellulose

PNIPAAm: Poly (N-isopropylacrylamide)

RHAMM: Receptor Hyaluronan Mediated Motility

CS: Chitosan

Chapter 1: Introduction

1.1 Background

Worldwide diabetes mellitus is now one of the focal concerns as it decreases longevity and increases mortality. Though the prevalence of diabetes has declined in many regions, it is still the leading public health concern. The International Diabetes Federation (IDF) estimates that there were roughly 451 million diabetic patients globally in 2017 and that number might increase to as many as 693 million by the year 2045 if prevention measures are not implemented. The cases of diabetes rose incredibly in the year from 1990 to 2017. In 1990, the incidence of diabetes was 11.3 million and it increased dramatically in the next two decades and is estimated around 22.9million which is approximately an increase of 102.9%. In 1990, the diabetes prevalence was 211.2 million and it reached 476.0 million in 2017 which showed an increase of 129.7%. The death events from diabetes also increased from 0.61 million (1990) to 1.37million (2017) (Lin et al., 2020).

All wounds lead to very severe health issues for patients who suffer from diabetes and need impactful treatment to be cured. If treatment is not done properly, then even minor cuts or injuries have the potential to worsen a patient's situation. Wounds that are categorized in diabetics patients are mostly topical wounds (foot ulcers, skin ulcers, arterial ulcers) and take longer time to heal than normal wounds. Wounds can be categorized into two different types: chronic and acute. Acute wounds are surgical or traumatic wounds and these types of wounds have a normal process of healing cascade. However, diabetic wounds are known as chronic wounds since they take longer time to heal than normal wounds also because of frequent destruction mechanisms of the regeneration of normal skin as well as face challenges for the wound to recover normally physiologically. This type of diabetic wounds gets influenced by increased blood glucose level, inappropriate inflammatory response, the significance of oxidative stress and risk of infection from bacteria (Wang et al., 2021a).

Infection is the primary challenge in wound healing and pathogens and microbes can invade more easily through the injured skin. There are multiple different wound healing events due to several categories of wounds. It becomes important to choose the proper wound dressing after figuring out the state of wounds (Opt Veld et al., 2020). Especially diabetes affects the wound healing cascade by obstructing the balance of the vessel growth and the proliferation phase (Okonkwo & Dipietro, 2017). Due to this, the wound healing process gets prolonged and chronic wounds and non-healing ulcers occur and the results can be fatal. These non-healing ulcers exhibit post complications to the patients including pain, infection-related dysfunction, even amputation and sepsis (Okonkwo & Dipietro, 2017).

Before the innovation of modern wound healing patches, dry dressing was the conventional way of dressing. Some commonly used ordinary dry dressing were- bandages, gauze to a limited extent, can be utilized to be absorbed in wound drainage and minimize wound infection. But these dry dressings are not so convenient to the wound healing process as they provide less effective reaction to improve wound environment as well as are unable to provide medication without interruption to speed up the healing process. When the moist wound healing theory comes up, then the use of these conventional dry dressings fades away and modern dressings get all the focus to get the responsive result. Hydrocolloids, Nanofibers, hydrogels and foams are only a few examples of the contemporary multifunctional wound dressings that have proven to be highly effective in treating diabetic wounds. Among all of these, hydrogels get the most priority here since they have the vigorous capacity of liquid absorption due to their formation with three-dimensional networks and facilitate the clinical use to treat wounds of diabetic patients and many experimentation purposes (Wang et al., 2021b).

1.2 Significance

There are some requirements needed to maintain appropriate wound dressings like moisture content, thermal resistance, protection against bacteria, enable gaseous changes, proper sterilization, host friendly and easily removable and so on. As all these criteria are available in hydrogels that's why it is known as a good dressing process (Opt Veld et al., 2020). The elements that the hydrogels are made up of are usually polymer based and these polymers can be natural or may found in lab and to accelerate the wound healing cascade. Many hydrogel patches deliver advantages like more integrated and improved treatment of the wounds, lessened the time required to heal the wound and thus reduction of the time of hospitalization and the cost of healthcare. They also have similarities with the living tissue and thus make it more compatible for providing more integrated applications in biomedical care (Tavakoli & Klar, 2020).

1.3 Aim

The aim of this thesis paper is to discuss the potential of natural polymer-based hydrogels in wound healing and management of diabetic patients wound recovery as well as in the progress of chronic healing for patients' convenience.

1.4 Objective

The main objective is to have an overview of naturally obtained polymer of hydrogel-based dressing, works by providing moist control environment conducive to wound healing as well as elimination of excess wastage from the wound site which makes the wound faster to heal also in terms of diabetic patient. In the chronic healing process, they can help through deliver drugs, peptides, growth factors which are essential for faster the healing procedure. These polymers contain anti-inflammatory, antioxidant, infection reduction properties which make them prominent to use in diabetic wounds or one have weak progress of healing. Moreover, this polymer-based hydrogel improve healing by integrating natural and accessible resources in the sake of healing management in diabetics.

Chapter 2: Methodology

Scholarly articles about natural polymer or biopolymer-based hydrogel and the disease of interest, in the diabetic patients wound healing process, were found using reliable online scientific literature sources like Google Scholar and PubMed of the National Library of Medicine. Searching the term biopolymer-based hydrogel which are naturally derived and diabetic patients wound healing process as it is a chronic disease by using PubMed's Advanced Search Builder https://pubmed.ncbi.nlm.nih.gov/ to find authentic information on related topics. After search on this, in first attempt without applied any limitations 234 results were shown from 2001-2023. After filtering 'clinical trial' and 'review' as article type, 74 research works were found. Then some more articles were found after filtering 'randomized control trial' and 'systemic review' on that particular topic. Also after looking for diabetic or chronic wound healing through hydrogel, there were 54 results appeared after put a choice on 'clinical trial', 'randomized trial' and 'review' as article type. Some others journals articles were used to have a strong authorization and to gather more information regarding this topic. Some renowned journals like Elsevier, Biomaterials Science these supportive journals were used for more clear thinking. A wide range of scientific journal articles were analyzed in order to acquire significant, up-to-date data and materials. This resource helped to address research issues with chronic wound healing of using biopolymer hydrogels. Then, a systematic compilation of this study's synthesized information was performed. The software Mendeley Desktop version was used to properly credit and cite all information obtained from various sources in accordance with the APA 7th referencing style.

Chapter 3: Wound healing

3.1. Normal wound healing progression

In healthy individuals, the wound heals through a cascade of steps. There are four steps in the complicated process of a wound healing: hemostasis, proliferation, inflammation and remodeling (Okonkwo & Dipietro, 2017).

Hemostasis: Hemostasis, which is defined by the formation of a provisional wound matrix, commences the wound healing cascade. In consequence to endothelial damage, components of the extracellular matrix attach to and activate platelets. Damaged tissues and aggregated platelets induce the extrinsic and intrinsic route. The combined efforts of the routes stabilize the fibrin and platelet clot. This leads in the creation of a structure through which wound-healing cascade cells move and multiply. In addition, it works as a repository for growth factors and cytokines (Zhao et al., 2016).

Inflammation: The subsequent phase of the wound recovery cascade is the inflammatory phase, which involves the lysis of cells and elimination of debris, including cellular, extracellular, and pathogenic material (Zhao et al., 2016). This phase is marked by an influx of inflammatory cells that stimulates the wound's pro-angiogenic chemicals. Chemokines implicated in the inflammatory response are related with the removal of dead cells, foreign substances and debris from the wound by recruiting inflammatory cells. In addition, they facilitate the motility, proliferation, and differentiation of endothelial cells, keratinocytes and their progenitor cells to ensure wound closure (Guo & DiPietro, 2010).

Proliferation: In the wound region, the number of endothelial cells, keratinocytes, and fibroblasts rises. They produce a transient extracellular matrix. Through the reduction of inflammatory cells, they also enable the re-epithelialization necessary to seal the wound.

Numerous pro-angiogenic chemokines, such as CXCL1, CXCL2, etc., promote the robust migration and proliferation of cells in wounds (Guo & DiPietro, 2010).

Remodeling: In the completion of the wound healing cascade, the cytokines TGB-beta, fibroblast, and myofibroblast stimulate the expression of alpha-smooth muscle actin, which then converts into myofibroblasts. Using their receptors, the myofibroblasts compress the wound. When type I collagen expression increases and MMPS lysis leads type III collagen to become disordered. A natural scar is the result of a balance between the creation of new collagen and the decomposition of old collagen. In the scar, the type I phenotypic collagen is rearranged. The end of the healing cascade is denoted by the apoptosis of vascular cells and myofibroblast (Zhao et al., 2016).

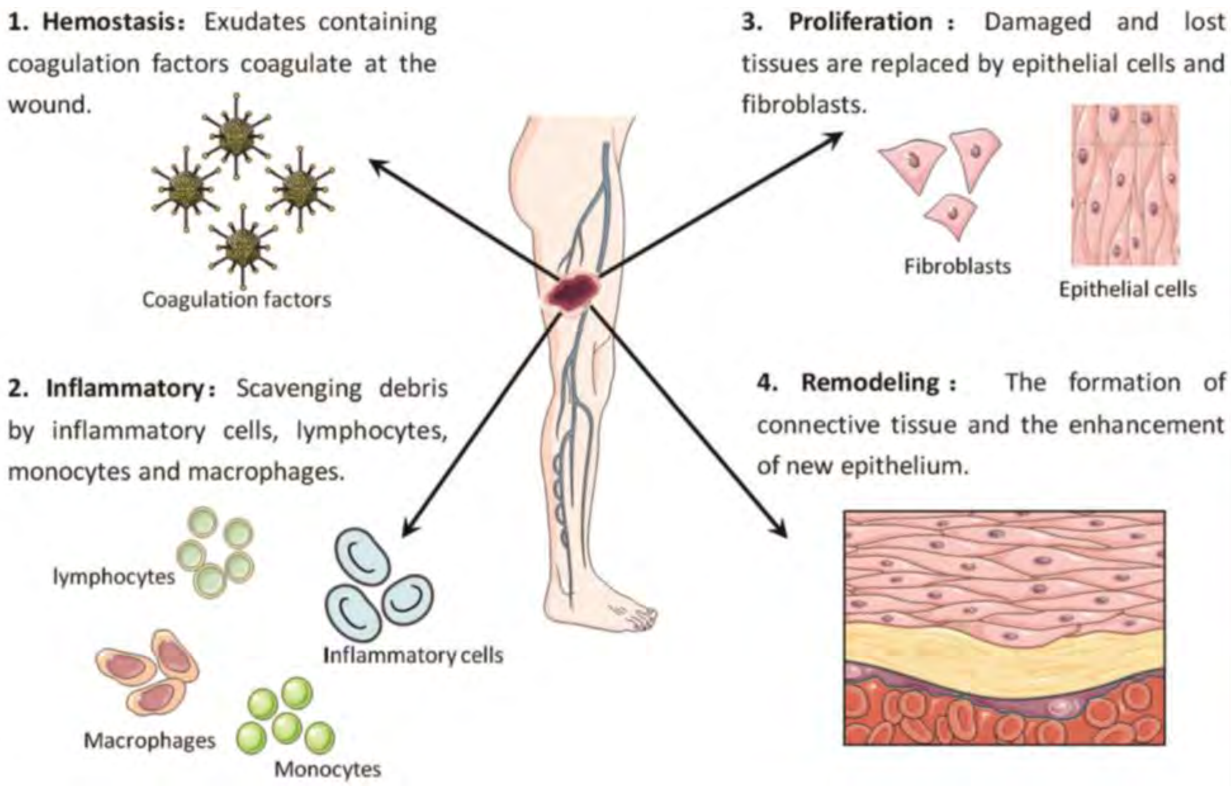

Figure 01: *A Demonstration of four wound healing stages: 1) hemostasis, 2) inflammatory, 3) proliferation, 4) remodeling*(Wang et al., 2021a)

3.2. Aspects influencing diabetic wound healing

Clinical and experimental studies show that diabetic wounds and other similar long-term injuries don't seem to heal in the same order as acute wounds. As previously mentioned, wound healing may block in a particular stage of the process, hence extending healing time and placing a significant burden on the life span of the patient (Shah et al., 2019).

Vasculopathy: Type-1 diabetes is accompanied with macrovascular disease, and compared to non-diabetic patients, the peripheral arteries are unable to transport nutrients and oxygen to the injured area effectively, resulting in delayed wound healing. These microcirculatory deficiencies are present in the earliest stages of diabetes (Karri et al., 2016). In add on to these microcirculatory deficiencies, endothelial cell disruption also develops, which may diminish vital physiological activity, such as that of nitric oxide synthase (Shah et al., 2019).

Neuropathy: Patients with diabetes are unable to recognize external stimuli such heat, wounds and pressure due to sensory deficiencies, due to this factor it may take longer time to heal the wound. Pathogenesis due to lack of pain and inconsistent vasodilator autoregulation slows wound healing and diminishes pressure detection. Therefore, neuropathy influences the progress of infection and bacterial load in tissues (Shah et al., 2019).

Infection: In the worsening of condition of diabetic patients' ulcer, infection is often responsible. Infections are a substantial reason for mortality in patients, resulting in amputation, and impaired recovery. Excessive bacterial load without the traditional indications of infection is also detrimental to the healing of wounds, ulcers and traumas (Shah et al., 2019).

3.3. Properties of hydrogel & biopolymers:

The three-dimensional (3D), hydrophilic, polymeric networks that are useful in terms of absorption of a great quantity of water or biological fluids is called hydrogel (Garg & Garg, 2016). This type of wound healing and dressing procedure, can soak up vast quantities of biofluids and water from the wound and make the wound heal faster. Hydrogels have been largely used for the purpose in wound dressing due to their strong permeability, input and output of different medications, adaptability, bioactivity, to provide the ability to debride and slough off necrotic tissue, increased water content, and create a humid environment. The benefits of hydrogels also include relaxing effects that increase patient compliance, the ability to moisten wound sites, and non-adherent (Alven & Aderibigbe, 2020). The potential features of hydrogel are- high water content, soft consistency, porosity, ability of simulating living tissue, low tensile strength, robustness and steadiness, biodegradability without generating toxic species, colorless, odorless, biocompatible and non-toxic, re-wetting competency, photo stability, pH-neutrality, required particle size and absorption etc (Garg & Garg, 2016).

Biopolymers are made from organic materials including plants, animals, and microorganisms. As they are biodegradable it affects their physicochemical composition and activity including drug releasing patterns and surrounding tissues interaction. Chitosan, cellulose, alginate and hyaluronic acid are few examples of biopolymers which are frequently used to prepare wound dressing (Alven & Aderibigbe, 2020)**.** Due to their low mechanical performance and instability of biopolymer-based systems, only few biomedical applications are possible. Though there are some drawbacks of biopolymer-based hydrogel but have some advantages as well, they have unique biochemical properties which are bioactive and, have their function in human body and in vivo (Neffe et al., 2013).

Chapter 4: Chitosan and Chitosan-based Hydrogel

4.1. Sources of Chitosan and its availability

The polymers used and their interconnections within the network are crucial factors in determining the properties of hydrogels (H. Liu et al., 2018). Chitosan is one of those hydrogel polymers which plays a significant role in wound healing through drug delivery. Natural amino polysaccharide is chitosan and it can be derived from the alkaline N-deacetylation of chitin (Hussain et al., 2017). The source of chitosan is natural chitin polysaccharide and this biopolymer is mostly available in various living things which are mostly insects and can be obtained through synthesize. Though chitosan can be derived from nature but can also be obtained from synthetic processes in the alkaline environment by deacetylation of chitin. On the other hand, budget friendly production of chitosan polymer is formed from the cell walls of fungi using the fermentation process. Chitosan has a sensitive amino group and its reactivity makes chitosan the only natural cationic polymer and thus has several implementations. It quickens the healing process of wounds and has antibacterial, antimicrobial, anti-tumor, anticoagulant, antifungal, and blood coagulation properties (H. Liu et al., 2018). Chitosan contains some features that makes it ideal for hydrogel production in wound healing as it is non-toxic, biodegradable, has adhesive property, biocompatible and give biological efficacy. To work as antibacterial properties chitosan, interact more with negative charge components in bacterial membranes like nucleic acid, protein, polysaccharide and give its effect against bacteria (H. Liu et al., 2018).

4.2. Function and application of chitosan hydrogel in diabetic patient

Wound healing is the combination of many processes which involves many cells and different molecules. In the wound healing stages coagulation is one of the primary stages in the healing process here chitosan can be helpful as it can speed up blood coagulation and thrombosis. It also works as a hemostat which is natural blood clotting and reduces pain by blocking nerve endings. In the inflammatory phase of wound healing chitosan create optimal inflammatory setting for healing. Chitin as well as chitosan in large concentration influence growth factor which release from platelets in the proliferation stage of wound healing. In regarding scar prevention and faster wound healing chitosan-based hydrogel help through collagen deposition, angiogenesis and boost up the formation of natural hyaluronic acid in the site of injury. Except of this function of wound healing chitosan hydrogel served as a barrier to prevent microbial intrusion and multiplication as well as a framework for cell growth. In addition, these types of hydrogels can work as drug delivery system by loading some active material like antibacterial, stem cells, growth factors and anti-inflammatory agents (H. Liu et al., 2018).

For diabetic patient, small injuries may result in a very serious issue which inhibit the formation of structure within proper time. According to the author N. Masood et al., silver nano particle has their ability to work as anti-inflammatory, antioxidant, antibacterial, antiviral, anti-angiogenesis. Here alone with silver nanoparticle natural chitin material, chitosan is used as efficient material in healing process. On the other hand, polyethylene glycol (PEG) has protein resistance, bio-compatible and nontoxic material. Due to have the water absorption properties hydrogel can imitate the environment for cells and tissue growth. According to an article the effects of silver nanoparticles and PEG in a combination and in the form of hydrogel has been examine on diabetic rats and can consider as very prominent healing material for diabetic chronic wounds(Masood et al., 2019).

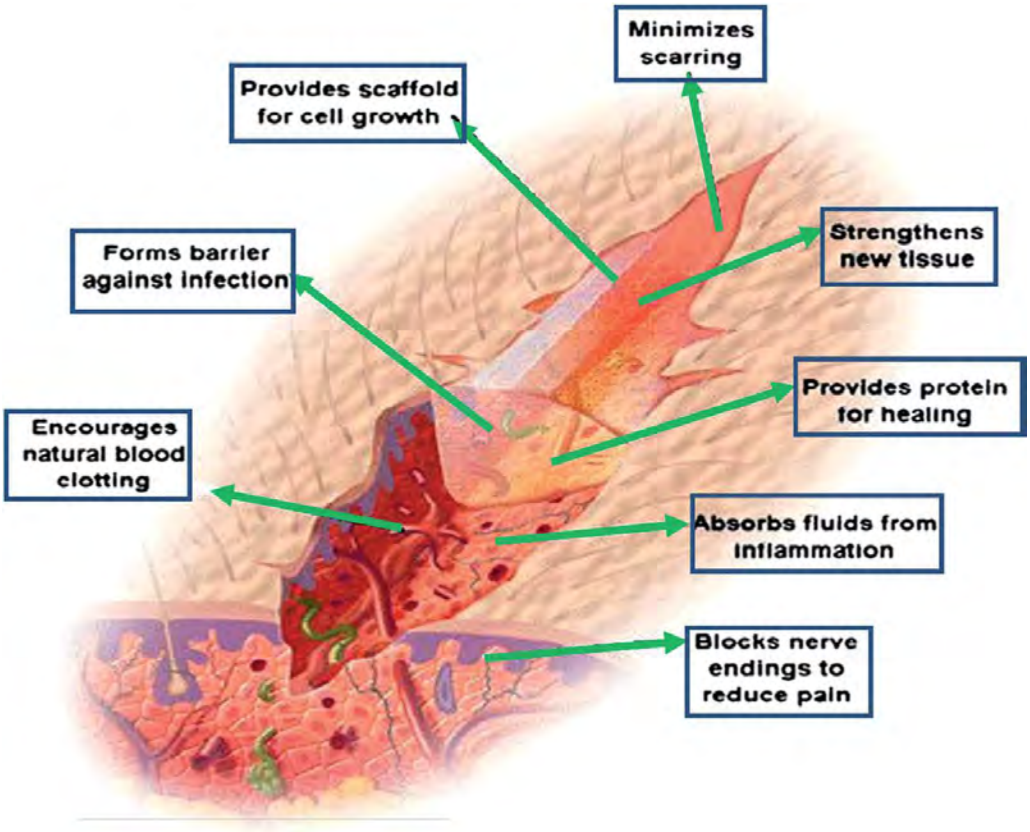

Figure 02: Chitosan based hydrogels roles in speeding up the healing process of wounds (H. Liu et al., 2018).

4.3. Chitosan based hydrogels as a drug delivery system

Chitosan could expedite the healing of acute wounds, but chronic wounds require a different treatment. Thus, slow release of medicinal payload may provide a more effective therapy (Bhattarai et al., 2010). Despite the fact that a significant number of active chemicals potentially serve as therapies for wound healing, the wound's inflammatory condition prevents the medicine from promoting healing, and some of the candidates have demonstrated clinical efficacy (Kidane & Bhatt, 2005). Smart delivery using chitosan hydrogels can load growth factors, antimicrobial drugs, peptides and stem cells to balance inflamed biochemical processes in chronic wounds and enhance healing. As a DDS, the efficiency of hydrogels made from chitosan depends not only on the chemical and physical characteristics of the gel, but also on how the medications are loaded into the hydrogels. There are three principal methods to load a drug: entrapment, covalent bonding and permeation (diffusion) (H. Liu et al., 2018). Though this procedure has its own efficiency and drawbacks but in terms of making hydrogel there are some considerations of network and drug properties which are need to be maintained to have proper wound healing result.

In delivery of drug properties like antimicrobial agents, stem cell delivery, growth factors delivery helps in the development of wound healing procedure. In terms of antimicrobial agents- tetracycline hydrochloride was incorporated into chitosan hydrogel which works as antibacterial and scar preventing dressing agents. This hydrogel dressing gives good outcome, chitosan improved wound healing with little scarring, whereas tetracycline hydrochloride defended against bacterial invasions (Anjum et al., 2016). Other antibacterial agents like Ag^+ ion, nano silver (nAg) (Rai et al., 2009), zinc oxide (ZnO) (Pelgrift & Friedman, 2013) give effective antibacterial properties and has a good biocompatibility as well as potential wound dressings.

In deliver of growth factors through hydrogel, where growth factors are known as peptides produced by inflammatory cells, endothelial cells, fibroblast and platelets. The production of extracellular matrix (ECM) can be stimulated by growth factors, which can also cause cell migration, proliferation, and differentiation (Guo & DiPietro, 2010). In comparison to normal wound healing, chronic wounds release fewer growth factors at various stages. In case of diabetic ulcers, a number of processes reduce peripheral blood supply and regional angiogenesis, all of which might impede wound healing (Brem & Tomic-Canic, 2007).

Through chitosan hydrogel DDS peptides can also be delivered like growth factors and stem cells. In spite of the fact that stem cells and growth regulators aim to enhance angiogenesis and restoration of epithelium, cost and safety concerns persist with their uses. Peptides offer effects similar with growth factors, but have cheaper cost and controlled features (Hosseinkhani et al., 2006). The role of chitosan in angiogenesis and restoration of epithelium of skin was greatly improved by peptide-modified chitosan hydrogel (Chen et al., 2015).

In delivery of other drugs, chitosan-based hydrogel has the effective progress in delivery of anti-inflammatory medications, amino acids, antioxidants, vitamins all of which lower the inflammatory response, nourish damaged tissue and improve wound healing (H. Liu et al., 2018). It was observed that a Chitosan–PVA hydrogel containing bee venom displayed anti-inflammatory properties. In diabetic rats, chitosan and bee venom composite greatly speeds up wound healing (Amin & Abdel-Raheem, 2014). In antioxidant drug delivery with chitosan-based hydrogel, antioxidants like nitric oxide, hydrogen peroxide these agents stimulate the activity of antibacterial, fibroblast proliferation, collagen synthesis and wound healing (Kim et al., 2015).

Chapter 5: Cellulose and Cellulose based hydrogel

5.1. Structure and source of cellulose and its biodegradability

The most prominent naturally produced glucose polymer is cellulose which can be used as natural polymer-based hydrogel in wound dressing can be found in natural plants and fabric. By the process of cellulose etherification, where hydroxyl groups of cellulose interact with organic compounds, produces most of the water soluble of cellulose derivatives. Cellulose interact with ether and ester derivatives produces methyl cellulose, ethyl cellulose, cellulose acetate, acetate trimellitate. In the pharmaceutical industry, cellulose ester derivatives are also utilized due to their distinct functional characteristics (Kabir et al., 2018). Cellulose based products have lower inflammatory response to the foreign entities and thus they are regarded as biocompatible and largely used in the production of hydrogel in wound healing (H. Liu et al., 2018). Composite hydrogels of cellulose can be obtained by mixing of synthetic and natural polymer with cellulose derivatives like chitin, chitosan, starch and so on. Different types of cellulose are available- bacterial cellulose (BC), plant cellulose (PC) is one of them. Plant cellulose (PC) and microbial or bacterial cellulose (BC) have the exact same chemical makeup but having differing macromolecular structures and physical characteristics. In regard of bacterial cellulose, it is known as totally pure compound but plant cellulose usually consists of various biogenic substances. Therefore, bacterial cellulose can be used as it is synthesized from bacteria but plant cellulose needs to purified and updated more. As a result of being biodegradable by a variety of bacteria and fungus found in soil, water, and the air, cellulose and its derivatives are environmentally beneficial. Furthermore, low levels of crystallinity and great water solubility of cellulose mainly results in speeds up biodegradation rate (Sannino et al., 2009).

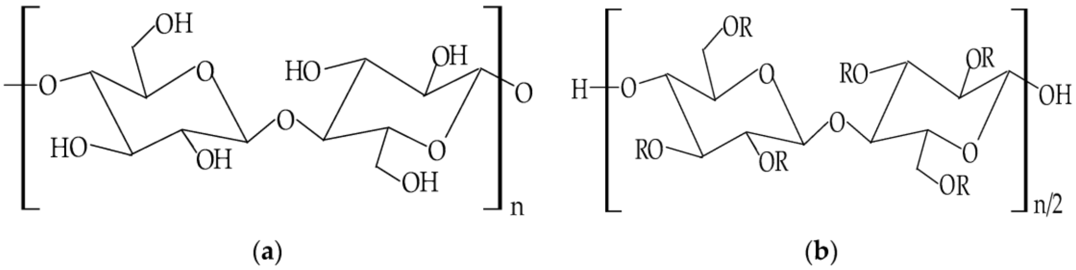

Figure 03: Structural formula of: (a) cellulose; (b) cellulose derivatives (Tudoroiu et al., 2021).

5.2. Hydrogels made of cellulose with crosslinking techniques

By chemically or physically stabilizing cellulose aqueous solutions, it is possible to get cellulose-based hydrogels. To get specific properties in composite hydrogels, extra polymer, which can be synthetic or natural can include with cellulose. In this crosslinking technique, the temperature may have an importance. As in less temperature, the solution of polymer chains gets hydrated and become knotted with other polymer. But in increase in temperature, macromolecules slowly loss their ability to hydrate themselves and thus hydrogel network is created due to hydrophobic interactions between polymers. In the formation of stable cellulose-based network, chemical agents and physical treatments might be needed. The amount of crosslinking in the polymer network can be measured by the number of crosslinking sites per unit volume. A variety of crosslinking agents and catalysts can be utilized to create hydrogels, depending on the cellulose derivatives that are being used. Some examples of crosslinkers are- aldehyde and its derivatives, urea and its derivatives, multifunctional carboxylic acid. Some crosslinker agents are harmful at different environment, such as aldehyde gives high toxicity in their unreactive condition. To ensure the quality and bioactivity of finished hydrogel, toxic crosslinkers need to remove and also to maintain ecologically sound manufacturing process (Sannino et al., 2009).

5.3. Applications of cellulose derived hydrogels

Cellulose based hydrogels have broad accessibility, cost effective, biocompatible as well as ideal for hydrogel precursor materials in situations where necessary, thus it has wide applications in different fields. It has well absorbent capacity and has conventional use as absorbent in biomedical applications. These cellulose-based hydrogels have good moisture content ability and can effectively use in hydrogels which keep the moisture control in wound healing. Also, can be used in personal hygiene products to keep the skins health and comfort. On the other hand, as it has also the good water content capacity, it can be largely used in farming sector to reserve water in harvesting. These can be used as hydrogel granules to keep soil hydrate and now it has very much commercially availability as well (Sannino et al., 2009). Though there are several applications but it can also help to work in drug delivery efficiently to treat in the wound healing.

5.4. Cellulose based hydrogel in wound healing and diabetics

Hydrogels' porous shape, opacity, thermal conductivity, high mechanical qualities, transmission of water vapor rate, and barrier capabilities against microbes make them attractive for wound healing (Su et al., 2021). In a study found that thermosensitive hydrogels are made of cellulose nanocrystal (CMC) and poly(N-isopropylacrylamide) (PNIPAAm), this combination shows well mechanical characteristics of hydrogels. In this combination of hydrogel if metronidazole is incorporated than it can give effect in infected wound which will reduce bacterial wound infection severity (Zubik et al., 2017). Another cellulose can be used in hydrogel is bacterial cellulose (BC) which has significant wound dressing potential due to its mechanical features, crystalline structure, and water content. Combination of BC and 2,3 dialdehyde cellulose, loaded with therapeutic properties exhibited tolerance to *S. pneumoniae*, and *E. Coli* and enhanced fibroblast adherence and proliferation (Zubik et al., 2017). BC based wound dressing have many valuable features like relief from wound pain, removal of waste fluids from the wound environment, protection from infection and scaring of wounds, these make them excellent efficient to numerous different wound dressings (Sezer et al., 2019). Another cellulose-based hydrogel which has come to focus is carboxymethyl cellulose (CMC). It has been largely used due to its least expenses, minimal toxicity, biocompatibility and capability to absorb exudate. CMC hydrogels are useful for diabetic as it is experimented on mice model containing honey as a bioactive material where it gives efficacy in tissue regeneration as well as decrease in wound area (Abazari et al., 2021). These factors help in the healing process and accelerate wound healing through various research and development.

Chapter 6: Alginate-based hydrogels

6.1. Sources, properties and structure of alginate

Alginate is a biopolymer derived from brown colored algae that is weakly acidic and spontaneously generated. It is readily accessible, biodegradable, and harmless. Alginate wound dressings are distinguished by a humid environment and fewer bacterial infections, both of which are essential for wound healing. It is made up of different amounts of guluronate and mannuronate, depending on where it comes from. Alginates contain M and G residues in various amounts and sequences, which influence their physical characteristics and molecular weight. Either ionic crosslinking with cations or acid precipitation can result in the creation of alginate gels. Both methods are discussed further below. Alginate dressing can be manufactured by crosslinking its ionic solution by magnesium, calcium, lead, zinc, cobalt, manganese and other ions to produce a gel or by additional operations to form freeze-dried permeable sheets in the arrangement of fibrous and foam dressing. These dressings capture wound fluid and create gels which give the moist condition to the wound surrounding, reduce bacterial infections, promote re-epithelization and granular tissue creation. Additionally, proper purification is required because the presence of contaminants might potentially induce an immunomodulatory reaction (Aderibigbe & Buyana, 2018).

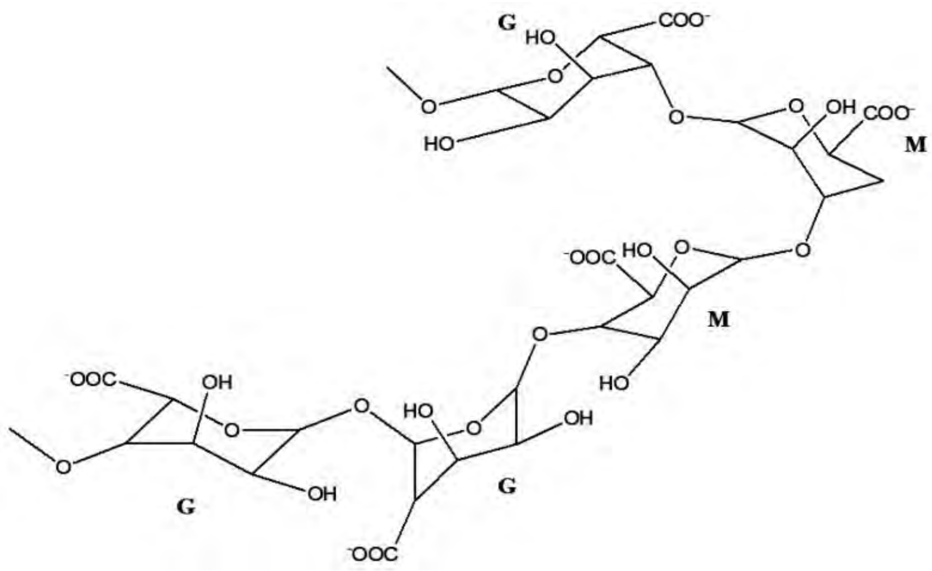

Figure 04: Structure of α-l-guluronic and β-d-mannuronic alginate residues (Aderibigbe & Buyana, 2018).

6.2. Methods of prepare hydrogel from alginate

Hydrogels are generally biocompatible because they are physically comparable to the macromolecular-based substances in the body and may often be administered into the body through nonsurgical administration. Hydrogels are often produced via chemical or physical cross-linking of hydrophilic polymers. There are variety of techniques for cross-linking alginate chains to create gels, as well as how these techniques affect the hydrogel qualities.

- **Ionic crosslinking:** Combining an aqueous alginate solution with ionic cross-linking compounds, like divalent cations which is the most typical approach for producing hydrogels from an aqueous alginate solution. It is assumed that the divalent cations attach exclusively to the place of the alginate chains where guluronate blocks are present. Then guluronate blocks of one polymer make links with those of neighboring polymer chains and that results the formation of gel structure. Commonly used ionic crosslinking agents for alginate is calcium chloride ($CaCl_2$). When utilizing divalent cations, the gelation rate is a crucial component in determining the gel's uniformity and strength, and delayed gelation results in structures with more uniformity and structural stability. One of the major limitations of ionically cross-linked alginate gels is their inadequate long-term durability under physiological settings because they gets dissolved in the surrounding environment by exchange process involving monovalent cations (K. Y. Lee & Mooney, 2012).

- **Covalent crosslinking:** Covalent cross-linking has received a lot of attention as a way to improve the unique properties of gels for a variety of applications, include tissue engineering. Water migration happens in covalently cross-linked gels as well, resulting in stress relief. In order to produce gels with a diverse range of mechanical attributes, the covalent cross-linking of alginate with poly-diamines of different molecular weights was first studied. Harmful covalent cross-linking reagents may necessitate rigorous removal of unreacted compounds from gels (K. Y. Lee & Mooney, 2012).
- **Thermal gelation:** In terms of thermal gelation, these types of hydrogels are now frequently used in many drugs delivery process because their inflammation properties are depended on temperature changes which leads to the modification of drug release from hydrogels. There are some importance of these type of hydrogels, they are often applied as most thermosensitive gels since they have the properties of their phase transition at body temperature. Alginate is not thermo-sensitive, hence few systems incorporating it have been documented in biological applications. At steady temperature, gel swelling ratio increased with sodium alginate concentration and decreased with temperature (K. Y. Lee & Mooney, 2012).
- **Cell crosslinking:** Contribution of cell in the formation of gel was ignored largely due to the formation of alginate gels. In this procedure the alginate will alternate and linked up with cell ligands with adhesion property, the capacity of cells to bind several

polymer chains can facilitate long-distance interaction. On the other hand, cell-cell interactions dominate in non-modified alginate solutions, thus cells aggregate and create a non-uniform structure. This technique is useful for tissue engineering cell delivery as it can transform into liquid to solidify agents when injected into the body. Through bond formation between cells and the attached ligands connected to the alginate chains, cells can contribute extra mechanical properties to alginate gels that seem to be ionically cross-linked to calcium ions (K. Y. Lee & Mooney, 2012).

6.3. Alginate based hydrogel in wound healing of diabetic patient

Hydrogels based on alginate have been explored for their possible implementation in diabetic wound healing. Alginate is a convenient material for use in wound dressings because of its excellent water-absorption capacity, biocompatibility, and biodegradability. One of the primary benefits of alginate hydrogels for diabetic wound healing is their capacity to maintain a moisture barrier at the wound site, which promotes wound healing. This can aid in the promotion of new tissue formation and lower the danger of infections. It has also been demonstrated that alginate-based hydrogels reduce inflammation and encourage the genesis of new blood vessels, which can assist in the process of healing. In diabetic patient the process of wound healing is multifaceted. Some key mechanisms that are used-

- Moist the area of wound healing: large quantities of water can be absorbed by hydrogels composed by alginate, generating a moist barrier at the wound site. By keeping the wound hydrate and lowering the chance of infection, this can stimulate the formation of new tissue. It helps in the healing process by the formation of new blood vessel in the maintenance of moist environment (Aderibigbe & Buyana, 2018).
- Tissue regeneration & tissue engineering: In tissue engineering technology and regenerative medicine process alginate hydrogels are performed as main framework in

most cases. The advancement of healing process mostly depends on the cell growth and proliferation. Alginate hydrogels can also imitate the extracellular matrix, which facilities the formation of new tissue (Sahoo & Biswal, 2021).

- Inflammation reduction: Alginate hydrogels in composition with other components (alginate hydrogels loaded with salicylic acid conjugates) gives anti-inflammation effect which progress the wound healing (Zhang & Zhao, 2020).
- Antimicrobial properties: These properties are also found in alginate-based hydrogels in composition with gallic acid, curcumin and other compounds which can stop the wound site infection (Zhang & Zhao, 2020).
- Drug delivery: Alginate hydrogels are also effective in drug delivery in the treatment of different issues. It can promote wound healing by accessing the body's natural wound healing process. It can deliver antibiotics, growth factor, enzymes which are required for wound healing and also diabetic patients required rug can be delivered through this procedure (Saghazadeh et al., 2018).

Chapter 7: Hyaluronic acid-based hydrogel

7.1. Sources & structure of hyaluronic acid

Another biopolymer based natural sources of hydrogel is hyaluronic acid (HA) which is known as immunoprotective, anionic non-sulfated glycosaminoglycans (GAGs). They are dispersed abundantly throughout brain tissues, synovial fluids, and connective tissues and are exceptionally hydrophilic biomaterials (Zamboni et al., 2018). HA is composed of β-d-gluconic acid and 2-acetamide-2-deoxy-a-D-glucose residues bonded to replace (1, 4) and (1, 3) glycosides. It has a greater capacity for water sorption, storage, and lubrication and influences many cellular processes such as adhesion, proliferation, and migration (Shah et al., 2019). HA is mostly found in the matrix of connective tissue, and mesenchymal cells make it to help organize the ECM of the tissue (Xu et al., 2012). Since it breaks down into simple sugars, it serves a crucial function in the fields of medicine and bioengineering. HA applied in various biomedical sectors like in surgery, tissue engineering and regeneration (Valachová et al., 2016). In the extracellular matrix (ECM) of the majority of tissues, the high molecular weight HA, together with other structural macromolecules, contributes to the network's mechanical stability (Xu et al., 2012). Inflammatory cells secrete higher quantities of matrix proteases and metalloproteinases (MMPs), which are a common chronic consequence. Proteoglycans, proteins, tissue constituents, and growth factors interact with HA, which is a crucial factor of wound healing (S. B. Lee et al., 2003). Because HA is biodegradable, biocompatible, non-immunogenic, bioactive, and non-thrombogenic, it’s a desirable component for the production of synthetic matrices for tissue regeneration. High concentrations of HA with a high molecular weight can create viscous molecular networks, HA solutions do not exhibit structural stability that is stable over time (Xu et al., 2012).

7.2. The function of hyaluronic acid in healing

It has been found that quickly after a wound appears, the presence of hyaluronic acid rises near the wound site. There are some vital factors served by hyaluronic acid which helps in the process of wound healing (Voigt & Driver, 2012). Because of its enormous molecular size, hyaluronic acid functions as a transient structure. HA interacts with keratinocytes which is a part of epidermis and forms strong junction to the skin. HA has an immediate effect on the proliferation and migration of certain cell types (Voigt & Driver, 2012).

Various receptors play important functions together with HA. One of those receptors of HA is CD44, can be found on virtually all mammalian cells. CD44 is important for the incorporation of HA breakdown products in the healing process and is a crucial receptor during the inflammatory response (Krolikoski et al., 2019). CD44 and HA, on the other hand, cannot function independently. CD44 then initiates a signaling cascade that aids in cell function and motility (P. Johnson et al., 2018).

Another receptor called the receptor for hyaluronan-mediated motility (RHAMM) contributes to the healing response induced by hyaluronic acid. Cellular movement are induced by the activation of the combined RHAMM and cytoskeletal proteins. These systems are crucial for tissue healing and inflammatory processes (Kouvidi et al., 2011).

Hyaluronic acid is present during all phases of wound healing. The molecular weight of HA can be used to determine its effect. Higher molecular weight of HA has the significance of giving anti-inflammatory effect whereas lower molecular weight stimulates inflammation (Filion & Phillips, 2010) Hyaluronic acid also exhibits antioxidative qualities, and it is considered that hyaluronic acid with a larger molecular weight can provide protection against the harmful effects of reactive oxygen species (Snetkov et al., 2020).

Hyaluronan transmission plays a significant function in the behavior of endothelial cells during angiogenesis. Larger molecular weight hyaluronic acid possesses antiangiogenic characteristics by limiting the proliferation and movement of endothelial cells (Slevin et al., 2007).

Chapter 8: Challenges of biopolymer-based hydrogel

8.1. Challenges in the hydrogel wound dressing

One major challenge that is mentioned is that hydrogels inadequate mechanical stability in the swelled state. But this problem can be addressed by using composite or hybrid hydrogels which is made up of several polymers in dressing formulations (Pan et al., 2021). The beneficial qualities of natural polysaccharides make them a viable treatment choice for chronic wounds but, a natural polysaccharide may provoke an unfavorable immune response and cause discomfort. The molecular weight regulation of the natural polysaccharide can be exploited to avoid such constraints (Cherng, 2019). If we look into the chitosan biopolymers, many studies demonstrated that molecular weight influences the functional features of chitosan and its derivatives which are used in the production of hydrogels. This is because molecular weight of chitosan mostly depends on the technique used to get chitosan from chitin and also its derivatives. Another topic of debate that may create some confusion is that whether or not these biopolymers have the potential to affect the physiological functions in terms of microbes' metabolism. This also depends on the molecular weight of that particular biopolymer. In terms of chitosan another important matter is combination of chitosan and CS derivatives with other polymers impacts their low toxicity (B. Rufato et al., 2019). Some of the qualities may have impact the wound healing process in dry sores. This may lead to dehydration, which reduces blood flow and the capacity of epithelial cells to migrate within the injured area, so preventing the formation of new tissue. Re-epithelization of wound area may hamper due to dry condition with natural polysaccharide dressing but it may faster under moist condition which will be maintained under adjustable molecular weight of polysaccharide. There are some common challenges that may be face when using hydrogel as wound dressings such as: if the capacity of absorption of wound liquid is not up to the mark, cannot be used in extreme exudative or infectious wound site, second layer of dressing may need in many cases when the dressing color is changed. These challenges are tried to overcome to make the great use of biopolymer-based hydrogel in wound healing benefits (Pastar et al., 2014).

8.2. Advancements to overcome challenges and new technologies

There are various methodologies for developing frameworks, which incorporate premade permeable platforms, decellularized extracellular grid, cell sheets with discharged extracellular network and cell typified in self-amassed hydrogel (Chan & Leong, 2008). Hydrogels frameworks are utilized in the recovery of cardiovascular tissues, ligament, and bone. For ligament tissue development, nanocellulose- and sodium-alginate-based hydrogels can be calcium chloride-crosslinked (Al-Sabah et al., 2019). Other findings revealed that hydrogel made of gelatin, constructed with eggshell particles aids in the dissociation of prefill developed cells into osteoblast (Wu et al., 2019). Injectable hydrogels are more worthwhile than typical hydrogel scaffolds attributable to its simple filling of sporadic imperfections and it doesn't need complex surgeries. In situ hyaluronan hydrogel which is cross-linkable can be utilized for tissue designing purposes. Hyaluronan is the extracellular grid constituent, where it helps in cell bond, multiplication, and separation (Shu et al., 2004). Polyethylene glycol-adjusted with RGD themes is a photopolymerized injectable hydrogels used in situ for tissue designing in the bone (Kondiah et al., 2016). Several innovative technologies have been employed in the construction of hydrogel wound dressings, including:

- Crosslinking: It is a procedure that increases the hydrogel network's stability and mechanical qualities by strengthening its network (Parhi, 2017).

- Nanotechnology: The implementation of nanomaterials, such as graphene and silver nanoparticles, into hydrogel dressings improves their antibacterial characteristics and promotes wound healing through nanotechnology (Y. Liu et al., 2022).
- Smart hydrogels: These are hydrogels that may adjust their properties in reaction to stimuli such as fluctuates in temperature, pH, or ionic concentration. This increases wound healing and decreases discomfort (Bordbar-Khiabani & Gasik, 2022).
- 3D printing: This method allows for the exact and reproducible assembly of hydrogel wound dressings in a variety of sizes and shapes (Tsegay et al., 2022).
- Drug delivery systems: Hydrogel wound dressings can be developed to slowly distribute medications, such as antibiotics, to the wound site in order to promote wound healing and avoid infection (N. Johnson & Wang, 2015).

Chapter 9: Discussion

Hydrogels are at present broadly available as the most convenient dressing material that promote the moist, healing-friendly environment and eliminate excess exudate. Natural polymer-based hydrogel and its properties have a great impact on wound recovery mechanism which makes the patients treatment efficient to recover specially in chronic healing. In diabetic patient wound healing mechanism are not as fast as normal individuals. They have impaired wound healing progress. Healing of diabetic wound is a chronic healing process and it takes much longer time to recover from that particular wound. The main attributes that hamper the diabetic wound recovery are persistent bleeding, abnormal regulation of inflammation, inhibited cell proliferation, susceptibility to infection, and defective tissue reconstruction. These are the stages of wound healing process which hardly function normal regarding diabetic patients wound healing. Natural polymer and its derivatives which can be extracted from nature has their function of healing by absorbing wound exudate, help in normal cells growth, tissue structure alteration and work as dressing materials effectively. Properties of hydrogel are mostly favorable to healing process as they have 3D polymeric network, hydrophilicity, absorption ability create moist and efficient environment for wound healing. These hydrogels have the satisfactory effect and thus convenient to patient use. Biopolymers are those one which can be extract from nature and mostly organic such as plants, animals and microorganism source are mainly responsible on this. Some biopolymers which are discussed here and frequently consider convenient for hydrogel dressing materials are like alginate, chitosan, cellulose and hyaluronic acid. Among these, most abundant one is cellulose in nature and polymer of glucose, can obtain from plant origin. In regarding wound management, it helps a lot since it can use as composite hydrogel in combination with other natural polymers. In between bacterial and plant cellulose, bacterial cellulose is in frequent application as they are significantly used in wound dressings. Many drugs can be delivered through this cellulose-based hydrogel to reduce infection, modify fibroblast adherence, give clinical efficacy towards many microorganisms and so on. Another largely used is CMC hydrogel due its efficacy, availability and biocompatibility. Chitosan is another biopolymer derived from chitin and a natural amino polysaccharide and has a way of least expenses formation of hydrogel. It has the effectiveness on healing as well as has effective results on tumor, microbial, fungal and as coagulant. Chitosan has several functions as hydrogel and also have efficient effect on diabetic patients healing process as can be loaded with required drugs, growth factors and peptides. Algae as such alginate has some distinct characteristics to works as hydrogel. It has crosslinking preparation methods in terms of hydrogel and has efficacy in diabetic patients' treatment like providing moist environment, tissue repair and drug delivery. Hyaluronic acid is the other one gets from natural sources and work as various biomedical application as well as in hydrogel formation. It has high molecular weight and long stability which make it proficient to use as hydrogel in wound recovery. HA has receptor base working ability so give effect on various receptors, contribute in healing response and cell signaling cascade to heal the wound. It has the significance in antiinflammation, antioxidation and molecular size also matters in the efficacy range. At the end, future aspects were discussed here where some drawbacks of hydrogel and advanced or improve technology were discussed to have a better vision on this treatment form. Mechanical stability action, balance of molecular weight where, for different molecular weight, particular natural polymers give different performance on healing as well as chronic wound. Metabolically relevant physiological processes in microorganisms are also depend on molecular weight and extraction of natural polymer to be used. Some advance technologies and perspective are also discussed here for increasing the future use of hydrogels by removing obstacles.

Chapter 10: Conclusion

Hydrogels are an efficient and convenient dressing material for wound healing due to their properties such as 3D polymeric network, hydrophilicity, and absorption ability. Biopolymers or natural polymer are made an efficient role in the hydrogel wound recovery treatment. They have those properties like tissue growth, cell proliferation, regeneration these features make the healing process more enhance. Natural polymers- alginate, chitosan, cellulose, and hyaluronic acid, are commonly used in the formation of hydrogel dressings and have distinct characteristics that contribute to the healing process. Drugs are also incorporate into the body through hydrogels and give the prominent result that is needed for that particular disease. As chronic wound diabetes requires longer time in healing process, so hydrogels are used to faster the healing process by providing necessary environment to heal. Efficient drug delivery can be done which contribute in anti-inflammation, prevention of microbial attack, moist environment to heal, enhance tissue growth and management in the other such healing properties. The future of hydrogel use in wound management involves overcoming some drawbacks and improving technologies to enhance the effectiveness of hydrogel dressings.

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