Natural Biopolymers: Wound Care Applications

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Abstract
Various neutral, basic, acidic, and sulfated polysaccharides have been the focus of interest with respect to biomedical and wound care applications. They are produced in different forms in order to cover all chronic and acute wounds. These bioactive wound dressings act as a chemo-attractant and the process of healing can start straight away by providing a moist environment. A relatively comprehensive review of the function and requirements of wound management aids, their physical forms, and the structural features of the polysaccharides and a brief overview of selected commercially available products is the aim of this entry.

INTRODUCTION

Wound healing is a multifactorial, complicated, physiological process. Cellular and biochemical components as well as enzymatic pathways play pivotal roles during the repair and recovery of a wound tissue. Some natural polymers have excellent structural and physicochemical properties, making them suitable agents for different applications in medical care of which wound management aids are one of the most important and encouraging modality. A variety of neutral (e.g., cellulose), basic (e.g., chitin and chitosan), acidic [e.g., alginic acid and hyaluronic acid (HA)], and sulfated polysaccharides (e.g., heparin, chondroitin, dermatan and keratan sulfates) have been the focus of interest with respect to biomedical/wound care applications. Furthermore, various researchers have recently studied more unusual complex heteropolysaccharides, isolated from plant and microbial sources. Their studies have shown that these biopolymers possess potentially useful biological and/or physicochemical characteristics with respect to wound care applications. The present entry aims to conduct a relatively comprehensive review of the function and requirements of wound management aids, their physical forms, and the structural features of the polysaccharides that are usually employed for their preparation and synthesis. Furthermore, a brief overview of selected commercially available products, specifically hydrogels, their applications in wound care and dressings, the pioneering research and manufacturing companies are presented for each compound.

CELLULOSE

Introduction

Cellulose has various distinctive structural properties, making it an outstanding compound for different medical and industrial applications. This substance is the main component of the plant cell wall.[1]

Cellulose use started with the exploratory investigation at Johnson & Johnson[2] and has been applied for covering wounds.[3]

Partial oxidation of the primary hydroxyl groups on the anhydroglucose rings produced oxidized regenerated cellulose (ORC), which in turn can be used to synthesize monocarboxyl cellulose as a natural and topical biomaterial. Those ORC materials containing 16–24% carboxylic acid content act as an important class of biocompatible and bio-absorbable polymers, which are available in a sterilized knitted fabric or powder form and can be used to stop bleeding.

ORC polymers were developed and presented for the first time in the late 1930s (Fig. 1).[4]

Structure

The structure of cellulose is shown in Fig. 1.

Applications in Wound Care

Traditionally, skin tissue repair materials are absorbent and permeable agents. For example, gauze, a traditional dressing material, can adhere to desiccated wound surfaces and induce trauma on removal of the dressing. In recent years, various medical and cosmetic applications of bacterial cellulose (BC) synthesized from surface cultures have drawn plenty of research attention in this field. Various potentials of BC originate from the unique properties of this compound, such as high mechanical strength of its never-dried BC membrane. Furthermore, high liquid absorbency, biocompatibility, and hygienic nature of this compound

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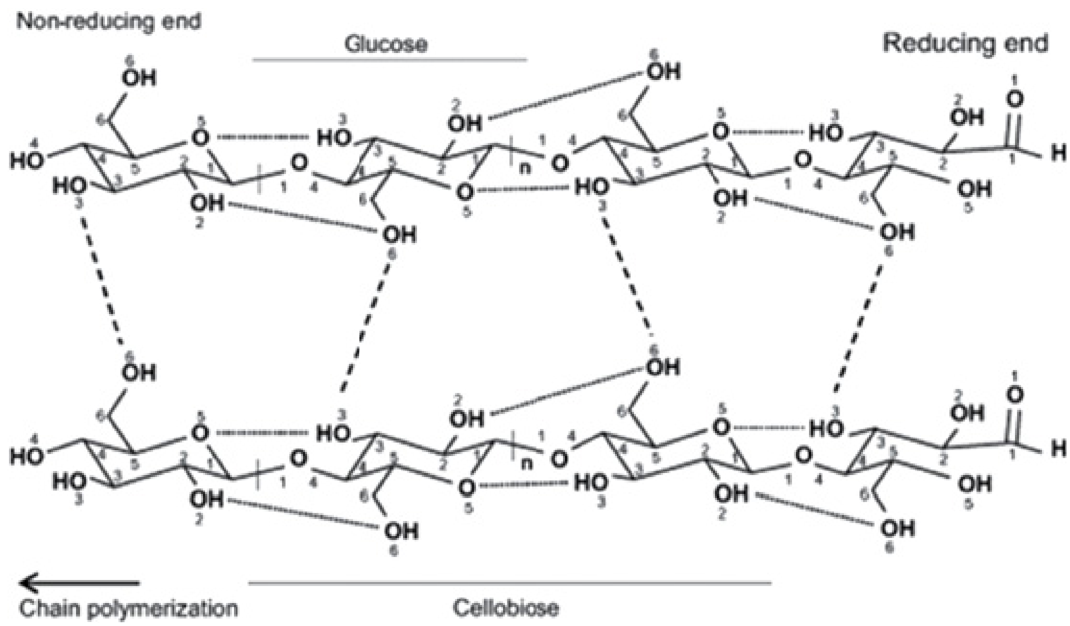

Fig. 1 The structure and the inter- and intra-chain hydrogen bonding pattern in cellulose I, dashed lines: inter-chain hydrogen bonding, Dotted lines: intra-chain hydrogen bonding.
Source: Reprinted from Festucci-Buselli,[1] Copyright 2007, with permission from Brazilian Society of Plant Physiology.

makes it an ideal option for specific demands of skin tissue repair.[3]

Manufacturing Companies

Johnson & Johnson Company is one of the pioneering groups in developing industrial-scale oxidation process using nitrogen dioxide to manufacture ORC-absorbable hemostat—Surgicel.

Cellulose Solutions Company produces Dermafill, Xylinum Cellulose—Cellulose Membrane Dressing.

CHITIN AND CHITOSAN

Introduction

Chitin is a copolymer of *N*-acetyl-glucosamine and *N*-glucosamine units randomly or block distributed throughout the biopolymer chain depending on the processing method used to derive the biopolymer. The biopolymer is termed chitin or chitosan when the number of *N*-acetyl-glucosamine or *N*-glucosamine units is higher than 50%, respectively. Chitosan has been more frequent studied because of its ready solubility in dilute acids, making it more accessible for use and chemical reactions.[5] However, it is normally insoluble in aqueous solutions above pH 7 because of its rigid crystalline structure and the deacetylation limiting its wide application.[6]

The main biochemical activities of the chitin- and chitosan-based materials are polymorphonuclear cell and fibroblast activation, cytokine production, giant cell migration, and stimulation of type IV collagen synthesis.[7]

Chitosan carries two types of reactive groups that can be grafted: first, the free amino groups on deacetylated units and, second, the hydroxyl groups on the C3 and C6 carbons on acetylated or deacetylated units. Grafting of chitosan facilitates the functional derivatives formation through covalent binding of a molecule, the graft, onto the chitosan backbone.[8]

The chitosan-based nanoparticles possess several advantages over the use of chitosan microspheres and microcapsules for drug-delivery process.[9]

Chitin and chitosan as sources of nutrients have antimicrobial activity with high resistance against environment conditions. Various studies have demonstrated the antimicrobial activity of these two compounds. Chitosan can efficiently control the growth of algae, and to inhibit in vivo and in vitro plant viral multiplication. Chitosan has been used as an antimicrobial compound through external application (exogenous) to the host, to the substrate or media, and to a physical surface containing microbial population. The chitosanase and chitinase are induced in plants as resistance mechanisms against pathogens, especially fungi. Some mechanisms for antifungal activity of exogenous chitosans are as follows:

- Induction of phenylpropanoid and octadecanoid pathways
- Induction of chitosanase
- Induction of chitosanase with many polypeptides
- Effect of chitosans on the plant enzymes in reaction to plant resistance against fungal pathogens

- Induction of phenolic compounds and/or phytoalexins
- Induction of morphological and/or physiological changes

In addition, some mechanisms suggested for understanding this antibacterial action are as follows:

- Reaction with bacterial teichoic acids, polyelectrolyte complexes
- Chelation of metals present in metalloenzymes
- Alteration of the bacterial adhesion
- Inhibition of the enzymes that link glucans to chitin
- Prevention of nutrients permeation.[10]

Structure

The structure of chitin and chitosan is shown in Fig. 2.

Application in Wound Care

Wound dressing is one of the most promising medical applications for chitin and chitosan. The adhesive nature of chitin and chitosan, as well as their antifungal and bactericidal traits, and finally their permeability to oxygen are the most important characteristics in improving the wound and burn treatment efficiency of the compound. Various derivatives of these two compounds have been proposed for wound treatment in the form of hydrogels, fibers, membranes, scaffolds, and sponges. The present entry aims to conduct a relatively comprehensive review on the wound dressing applications of biomaterials based on chitin, chitosan, and their derivatives in various forms.[12] In the field of veterinary medicine, chitosan has been proven to enhance the functions of polymorphonuclear leukocytes (PMNs) (phagocytosis, and production of osteopontin and leukotriene B4), macrophages (phagocytosis, and production of interleukin-1, transforming growth factor b1, and platelet-derived growth factor), and fibroblasts (interleukin-8 synthesis). Therefore, chitosan promotes granulation and organization, making it a beneficial agent for treating open wounds; certain PMN functions are enhanced, such as phagocytosis and the production of chemical mediators.[13]

Manufacturing Companies

ChitoTech Company was developed from a research facility for the study of natural biopolymers and their applications in medicine. ChitoHeal film and ChitoHeal Gel are two important chitosan-based dressings.

HemCon is now a world leader in advanced chitosan research and development, and continues to expand its application.

Medovent is the first company to overcome the technological barriers for processing chitin- and chitosan-based biopolymers; and aim to become a leading specialist for chitin- and chitosan-processing technologies to manufacture medical devices of complex designs with highest quality, reliability, and performance.

Medoderm is a world innovator in developing chitosan-based medical products.

ALGINATE

Introduction

Alginate is a collective term for a family of polysaccharides synthesized from brown algae and bacteria. Alginic acid was first discovered, extracted, and patented by Stanford.

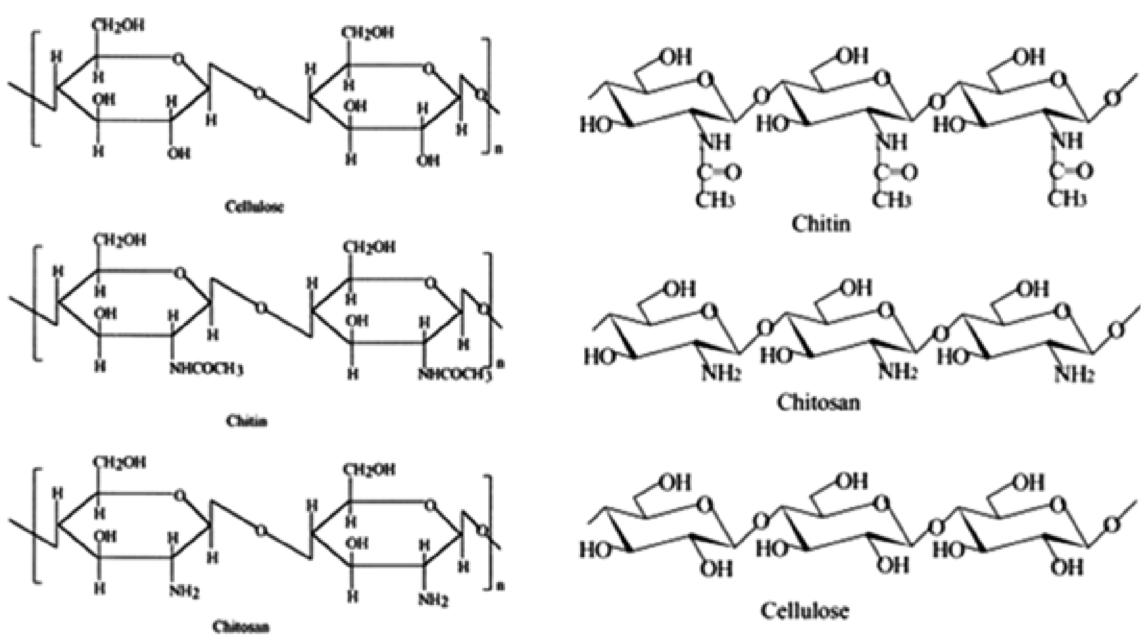

Fig. 2 Structures of cellulose, chitin and chitosan.
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This polysaccharide was recognized as a structural component of marine brown algae, constituting up to 40% of the dry matter and occurs mainly in the intercellular mucilage and algal cell wall as an insoluble mixture of calcium, magnesium, potassium, and sodium salts. The presence of alginate improves the mechanical strength and flexibility of the seaweed as well as acts as water reservoir preventing dehydration when a portion of seaweed is exposed to air. Therefore, alginate can be assumed to have the same morphophysiological properties in brown algae as those of cellulose and pectin in terrestrial plants. Several bacteria such as *Azotobacter vinelandii* and various species of pseudomonas produce an exocellular polymeric material that resembles alginate.

The stability of an alginate molecule is strongly dependent on conditions such as temperature, pH, and presence of contaminants. The glycosidic linkages between the sugar monomers of the polysaccharide are susceptible to cleavage in both acidic and alkaline media.[14]

Structure

Three fractions are traditionally isolated: two of these contain almost exclusively α-L-guluronic acid (G) and β-D-mannuronic acid (M) residues, respectively; the third one is composed of both uronic acids in almost equal proportion (Fig. 3).[14]

Applications in Wound Care

Alginate dressings are absorbent, nonadherent, biodegradable, nonwoven fibers derived from brown seaweed. They are composed of calcium salts of alginic acid and mannuronic and guluronic acids. Alginate dressings in contact with sodium-rich solutions such as wound drainage impose the calcium ions to undergo an exchange for the sodium ions, forming a soluble sodium alginate gel. This gel maintains a moist wound bed and supports a therapeutic healing environment. Alginates can absorb fluid 20 times their own weights that can vary based on the particular product. They are extremely beneficial in managing large draining cavity wounds, pressure cavity ulcers, vascular ulcers, surgical incisions, wound dehiscence, tunnels, sinus tracts, skin graft donor sites, exposed tendons, and infected wounds. Furthermore, their hemostatic and absorptive properties make them efficient treatments for bleeding wounds. Alginates are contraindicated for dry wounds, eschar-covered wounds, surgical implantation, or on third-degree burns. Alginates are available in various sizes and forms, including in sheet, pad, and rope. However, newer versions of calcium alginate dressings contain controlled release of ionic silver. They are usually changed daily or as indicated by the amount of drainage. Early wound care interventions may warrant more frequent dressing changes due to high volume of drainage. The frequency of dressing changes decreases as fluid management is reached.[15–18]

Manufacturing Companies

Coloplast Company produces Comfeel plus Ulcer Dressing, which is consisted of a semipermeable polyurethane film coated with a flexible, cross-linked adhesive mass containing sodium carboxymethylcellulose and calcium alginate as the principal absorbent and gel-forming agents.

Smith & Nephew Company produces Algisite M, which is a calcium–alginate dressing, forming a soft, integral gel in contact with wound exudate.

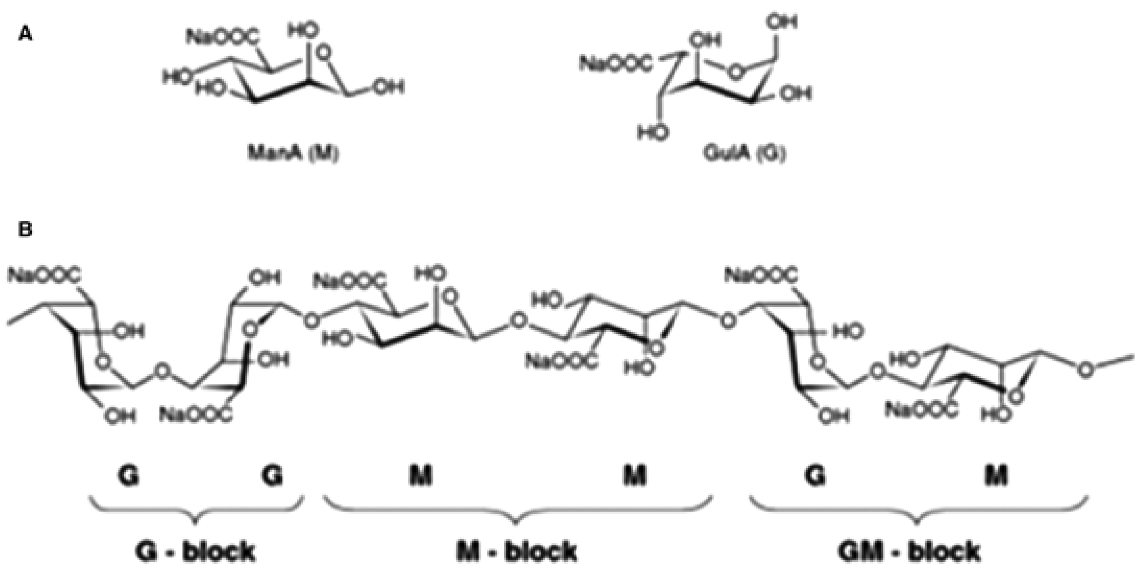

Fig. 3 Alginate chemical structure. (**A**) The 4C1 conformation of β-D-mannuronic acid (M) sodium salt and the 1C4 conformation of α-L-guluronic acid (G) sodium salt. (**B**) The block composition of alginate with G-blocks, M-blocks, and MG-blocks.
Source: Reprinted from Rehm,[14] Copyright 2009, with permission from Springer Science + Business Media.

STARCH

Introduction

Starch is a common constituent of higher plants and the major form of carbohydrates store. Starch in chloroplasts is in transitory state that accumulates during the light period to be utilized during the dark.[19]

Starch industries need high-amylose-content starch in great volume that is increasing by its unique functional properties.[20]

Structure

The structure of starch is shown in Fig. 4.

Applications in Wound Care

Starch is one of the most common and cost-effective polysaccharides. It usually includes about 30% amylose, a linear a-(1, 4) glucan, and 70% amylopectin, dendritically branched version. Chemically modified starches, enjoying outstanding properties such as lower cost and biodegradability, are finding various applications in industry. Various research teams have comprehensively studied chemical modifications of starch through graft copolymerization of vinyl monomers onto starch.[22,23] Polyvinyl alcohol (PVA)/starch blend hydrogels can be prepared by chemical cross-linking technique. Membranes synthesized through cross-linking of corn starch and PVA with glutaraldehyde have sufficient strength. The resulted hydrogel membrane can serve as artificial skin. Using these membranes, concurrently various nutrients or healing factors and medications can be delivered directly onto the site of action.[24]

Manufacturing Companies

PolyMem Dressings protect the wound and facilitate the body's natural healing process.

Aspen Medical Company is one of the pioneering companies with more than 25 years' experience in the medical device. Aquaform is a clear, viscous, sterile gel containing a modified starch polymer, glycerol, preservatives, and water.

Smith & Nephew Company produces Cadesorb, which is a white, starch-based sterile ointment that reduces local wound pH to around 5, thus modulating protease activities.

COLLAGEN

Introduction

Collagen type I is the most abundant proteins available in mammals. Its application in a range of tissues from tendons and ligaments, to skin, cornea, bone, and dentin improves mechanical stability, strength, and toughness. These tissues have quite different mechanical demands, some need to be elastic or to store mechanical energy, while the others need to be stiff and tough. This shows the versatility of collagen

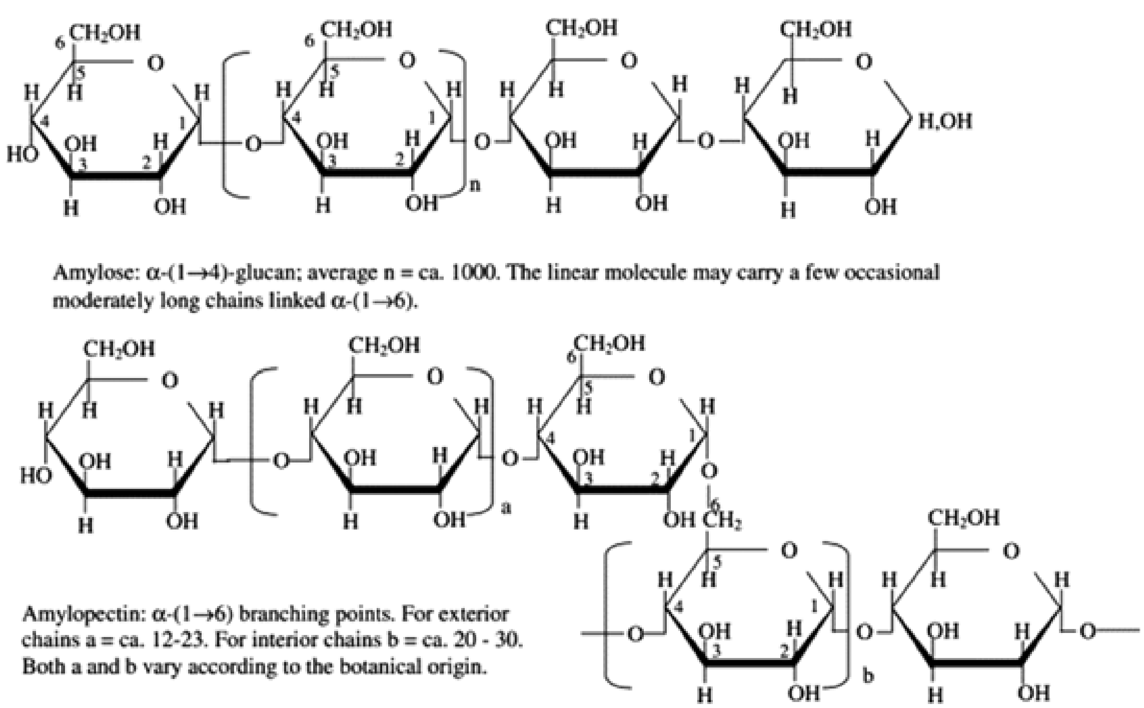

Fig. 4 Structure of amylose and amylopectin.
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as a building material. While in some cases, including bone and dentin, the stiffness is increased by the inclusion of mineral. In addition, the mechanical properties are adapted by a modification of the hierarchical structure rather than by a different chemical composition. The collagen fibril with 50 to a few hundred nanometer thickness is the basic building block of collagen-rich tissue. These fibrils are then assembled to a variety of more complex structures with very different mechanical properties. As in all collagens, each fibrillar collagen molecule consists of three polypeptide chains, called α chain. Molecules can be homotrimeric, consisting of three identical α chains, as in collagens II and III, or heterotypic, consisting of up three genetically distinct α chains. Individual α chain is identical by the following nomenclature: α n (N), where N is the Roman numeral indicating collagen type and n is the number of α chain.[25]

Structure

The structure of collagen is shown in Fig. 5.

Applications in Wound Care

Collagen is a major protein of the body that is necessary for wound healing and repairing process. Collagen dressings, derived from bovine hide (cowhide), are either 100% collagen or may be combined with alginates or other products. They are a highly absorptive, hydrophilic, and moist wound dressing. Collagen dressings can be used on granulating or necrotic wounds as well as on partial- or full-thickness wounds. A collagen dressing agent should be changed a minimum of every 7 days. If infection in wound is present, daily dressing change is recommended. Collagen dressings require a secondary dressing for securement.[27]

Manufacturing Companies

Johnson & Johnson Company produces Fibracol Plus. Advanced wound care dressing with 90% collagen composition.

Coloplast Woundres Collagen Hydrogel is the main component of skin and connective tissue playing a pivotal

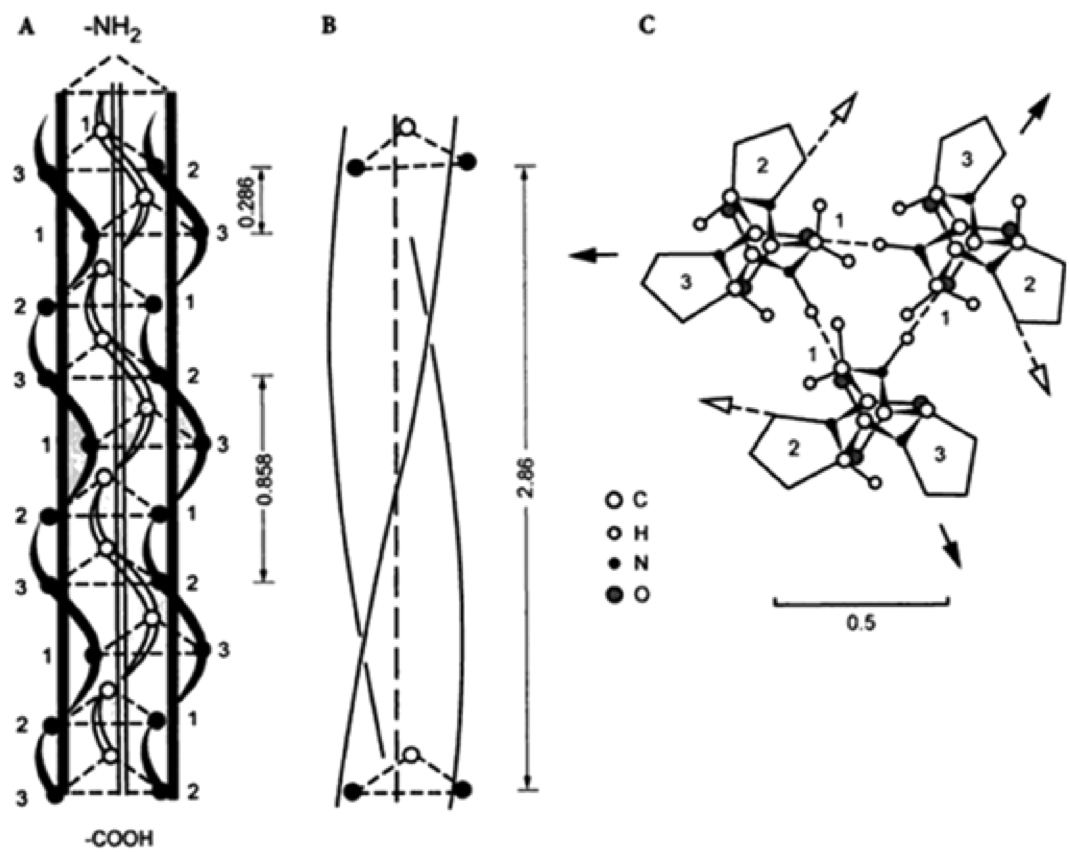

Fig. 5 Model of the collagen triple helix. The structure is shown for (Gly-Pro-Pro)$_n$ in which glycine is designated by 1, proline in X-position by 2 and proline in Y-position by 3: (**A, B**) side views. Three left-handed polyproline-II-type helices are arranged in parallel. For clarity, the right-handed supercoil of the triple helix is not shown in (**A**) but indicated in (**B**). Dashed lines indicate positions of C-atoms (and not hydrogen bonds as in (**C**)). All indicated values for axial repeats correspond to the supercoiled situation; (**C**) top view in the direction of the helix axis. The three claims are connected by hydrogen bonds between the backbone NH of glycin and the backbone CO of proline in Y-position (dashed lines). Arrows indicate the directions in which other side chains than proline rings emerge from the helix. Approximate residue- to residue distances, repeats of the polyproline-II- and triple helix and a scale bar are indicated in nm.
Source: Reprinted from Fakirov,[28] Copyright 2007, with permission from Hanser Publications.

role in all phases of wound healing. It promotes autolytic debridement through rehydrating and softening dry wounds and necrotic tissue.

SILK

Introduction

Silk is a fibrous protein biopolymer with remarkable mechanical properties. Silk fibers belong to the group of secretion-type animal fibers.[28]

Historically, silkworm silk has been used commercially as biomedical sutures in repairing wound injuries. Furthermore, several studies have been conducted on the feasibility and application of this biomaterial in tissue engineering because of its slow degradation, excellent mechanical properties, and biocompatibility. The recent advances in technology have made it possible to fabricate silk-based materials with various geometries, including films, sponges, mats, and fibers, from purified silk fibroin solution.[29]

Its composition is a mix of an amorphous polymer, which makes it elastic, and chains of two of the simplest proteins, which make it tough. Out of 20 amino acids, only glycine and alanine serve as a primary constituent of silk. Fibroin consists of about 40% glycine and 25% alanine as the major amino acids. The remaining components are mostly glutamine, serine, leucine, valine, proline, tyrosine, and arginine. The high elasticity of spider silk is because of glycine-rich regions where several ordered multiple amino acids are continuously repeated. A 180° turn (α-turn) occurs after each sequence, resulting in α-spiral or α-helix structure. β-sheets act as a cross-link between the protein molecules where the regular structure of these sheets gives high tensile strength to spider silk.[30]

Structure

The structure of silk is shown in Fig. 6.

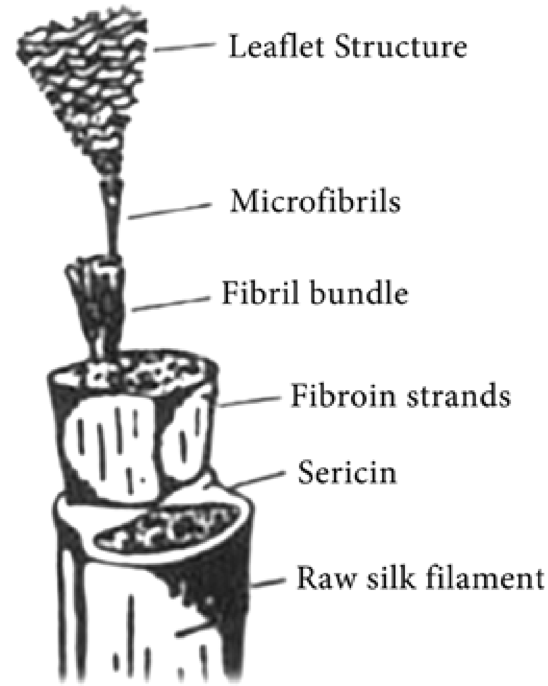

Fig. 6 The structure of raw silk fiber.
Source: This figure was published in Karmakar,[31] Copyright 1999, with permission from Elsevier.

Applications in Wound Care

Different studies have shown the wound-healing-facilitating properties of silk and its different derivatives. For instance, studies on animal mouse wound model have demonstrated high efficiency of silk protein–biomaterial wound dressings with epidermal growth factor (EGF) and silver sulfadiazine as a novel wound-healing agent[32] or silk fibroin/alginate-blended sponge for wound healing.[33]

Manufacturing Companies

Zhejiang Huikang Medicinal Articles and Wuxi Wemade Healthcare Products are the two main companies located in China that produce Medical Silk Adhesive Bandage. Furthermore, Jinhua Jingdi Medical Product Company in China produces Silk Medical Tape bandage.

HYALURONIC ACID

Introduction

Hyaluronan (known as HA or hyaluronate) is an anionic, nonsulfated glycosaminoglycan distributed widely throughout connective, epithelial, and neural tissues. HA is a big molecule, with molecular weight often reaching millions.[34] HA is an important component of articular cartilage, which coats around each cell (chondrocyte).[35]

As well as a major component of skin that plays an important role in tissue-repairing process.[36]

Structure

HA is a polymer of disaccharides, composed of D-glucuronic acid and D-*N*-acetylglucosamine, linked via alternating β-1,4 and β-1,3 glycosidic bonds (Fig. 7).[37]

Applications in Wound Care

HA is a naturally occurring polymer within the skin. It has been extensively studied since its discovery in 1934. It has been used extensively in a wide range of medical fields as diverse as orthopedics and cosmetic surgery. However; it is in tissue engineering that it has been primarily advanced for treatment. The breakdown products of this large macromolecule have a range of properties that lend it specifically to this setting as well as to the field of wound healing. It is

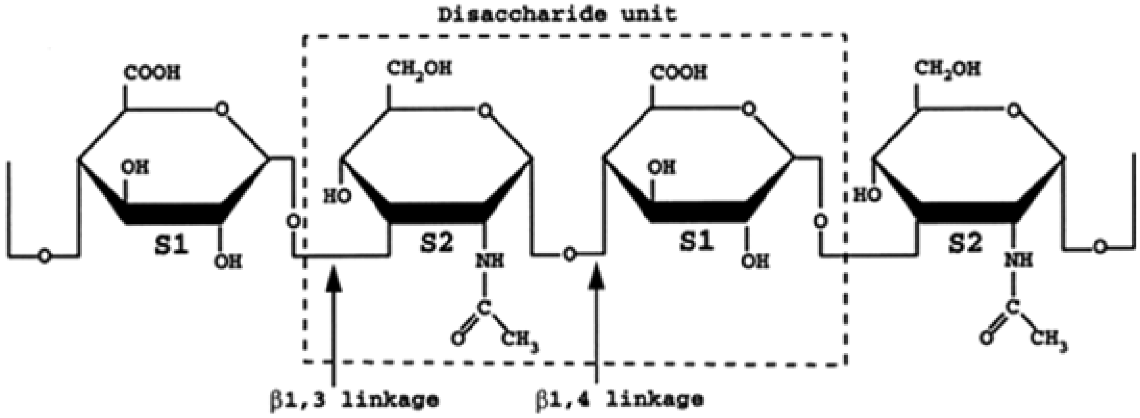

Fig. 7 The polymer is built from alternating units of glucuronic acid (S1) and *N*-acetyl glucosamine (S2). Stereo diagram of ribbon representation of the SpnHL protein with two bound disaccharide units (HA1 and HA2) of HA. The direction of HA1 is such that glucuronic acid residue (UA1) is the non-reducing end, which interacts with the Arg243, Arg300, and Arg355 and the *N*-acetyl glucosamine residue (NAc1) is the reducing end, which interacts with the key catalytic residue Tyr408.
Source: Reprinted from Ponnuraj,[38] Copyright 2000, with permission from Elsevier.

non-antigenic and may be manufactured in a number of forms, ranging from gels to sheets of solid material through to lightly woven meshes. Epidermal engraftment may be the best candidate among available biotechnologies so that has shown great promise in both animal and clinical studies of tissue engineering. Ongoing work centers on the ability of the molecule to enhance angiogenesis and the conversion of chronic wounds into acute wounds.[39]

Manufacturing Companies

Misonix Inc. produces Hyalofill®-F, which is an absorbent, soft, and conformable dressing composed of HYAFF® (HA ester) that provides a moist HA-enriched wound environment.

NovaMatrix™, a business unit of FMC BioPolymer (Philadelphia, PA, USA), produces and supplies well-characterized and documented ultrapure biocompatible and bioabsorbable biopolymers.

KERATIN

Introduction

The term "keratin" originally is referred to the broad category of insoluble proteins that associate as intermediate filaments (IFs) and form the bulk of cytoplasmic epithelia and epidermal appendageal structures. Researchers have classified mammalian keratins into two distinct groups based on their structure, function, and regulation: "hard" and "soft" keratins.[40]

Chains of amino acid groups are the primary structure of keratin proteins that vary in the number and sequence for different keratins. Its sequence influences the properties and functions of the keratin filament. All proteins that form IFs have a tripartite secondary structure.[41]

Structure

The structure of keratin is shown in Fig. 8.

Applications in Wound Care

The keratin dressings are called "gel," "matrix," and "foam." The gel can be used for dry exudate, the matrix for light-to-heavy exudates, and the foam for moderate-to-heavy exudate.[43]

Manufacturing Companies

Keraplast Technologies Company located in the US producing keragelT, keragel, keramatrix, kerasorb and keragelT deressings for wounds caused by Epidermolysis bullosa.

CONCLUSION

Wound healing is a multifactorial, complicated, physiological process that is prone to abnormalities. Various type of natural biopolymers including neutral (cellulose), basic (chitin and chitosan), acidic (alginic acid and HA), and sulfated polysaccharides (heparin, chondroitin, dermatan, and keratan sulfates) have been the focus of interest with respect to biomedical and wound care applications. The present entry presented a relatively comprehensive review on the most available and frequent use of biopolymers in the wound care applications, including cellulose, chitin and chitosan, alginate, starch, collagen, silk, HA, and finally keratin. Different aspects of these natural polymers were included in this entry, including a brief description of each compound, its composition, natural forms, structure, its applications in wound care, and famous companies

Fig. 8 α-Helical Structure, the organized protein structure, which forms approximately 30% of any - keratin.
Source: Reproduced with permission from Feughelman,[42] *Mechanical Properties and Structure of Alpha-Keratin Fibres: Wool, Human Hair and Related Fibres* by Max Feughelman (UNSWPress, Sydney, Australia, 1997).

pioneered in manufacturing of that biopolymer. Findings of the present review show the ever-increasing research interest on the development and applications of the natural biopolymers in different medical applications, especially in wound care applications.

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