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Chapter

Plant Macromolecules as Biomaterials for Wound Healing

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Abstract

Natural biomolecules are increasingly relevant for biomedical applications and tissue engineering for being able to produce an effect on chemical signals, organization of cells, and restitution of extracellular matrix in lesioned tissues. In this chapter, we will address the potential of plant macromolecules, in particular, carbohydrates and proteins such as hemicelluloses and lectins. While lectins are mostly carbohydrate-binding proteins, which can interact with cell surfaces to initiate anti-inflammatory pathways, as well as immunomodulatory functions, hemicelluloses are remarkably known by their ability to form viscous solutions even at low concentrations, which makes them an excellent candidate as vehicle to carry different sorts of biomolecules. Taking into account the complexity of the whole healing process, as an overlapping and coordinated cascade of events, most of the properties presented here by those materials may be of interest to the wound-care market.

Keywords: lectins, galactomannans, biomolecules, polysaccharides

1. Introduction

Skin is the largest organ, which presents a fairly robust arrangement, working as a natural shield against physical, chemical, and bacterial damage to the body. When it suffers any disruption in this arrangement by means of acute lesions, the skin goes through a fascinating repair process finalizing in wound closure and leaving some scars. This complex mechanism is dependent on many cell types and mediators

interacting to maintain the physiological regulation of skin [1, 2]. Chronic wound results in situations such as diabetes or vascular lesions, when defective skin usually persists causing the loss of integrity, and in some cases, the overlapping of structural layers, as well as delayed skin tissue recovery [3].

Human body tissues present a wide range of physical characteristics, which include stiffness and porosity. A multidisciplinary interface between areas such as cell biology, biotechnology, mechanics, materials science, bioengineering, and clinical research has been used to contribute significantly to tissue engineering. Many wound dressings have been developed seeking to restore and improve tissue function by generating new biocompatible substitutes or by rebuilding these tissues [4, 5]. However, these sorts of materials are quite costly, which might affect the widespread adoption.

From this perspective, an ideal wound dressing would maintain a microenvironment in the injured bed and would direct the specific healing properties for each type of wound or disease that affects the patient under treatment. The dressing should also keep the moisture balance, which works as a barrier of protection against infections and would provide thermal insulation for the wound [6]. Therefore, recent technologies for biomedical applications invest in the development of scaffolds able to mimic the natural environment for skin grown and regeneration after damage [4].

Polysaccharide-based biomaterials emerge in the field of tissue engineering, as they are mainly used as hydrogels for the effective treatment of wounds and skin burns. They can be categorized as neutral (e.g., glucans, dextran, and cellulose), acids (acid hyaluronic), basic (chitosan) or sulfated polysaccharides (heparin and chondroitin). The most popular and naturally produced biomaterials of polysaccharide origin are chitosan, hyaluronic acid, and alginate. These polysaccharides may also be subdivided into homopolysaccharides such as glucans, cellulose, dextran and chitosan, and heteropolysaccharides such as alginates, agarose, carrageenan, pectin, galactomannans and xyloglucans. All exhibit peculiar physicochemical properties and a considerable biocompatibility and biodegradability, and thus have important applications in biomedical fields [4].

In this chapter, we focus our attention to plant macromolecules such as carbohydrates and proteins (in particular hemicelluloses and lectins) as biomolecules for wound healing applications.

2. Wound healing

Wound healing is a critical, complex and highly coordinated process to maintain skin function. Immediately after injury, a multitude of molecular and cellular systems are activated to suspend blood loss, eliminate microorganisms and foreign materials, and recompose injured tissue [3]. These cellular and biochemical events in wound repair can be divided into the following steps: hemostasis, inflammatory response, cell proliferation and synthesis of the elements that make up the extracellular matrix (ECM), and the later period, called remodeling. These stages are not mutually exclusive but overlapping over time [7].

In physiological conditions, platelets circulate in the vicinity of the vascular walls and are activated when the continuity of the endothelial layer is ruptured and the underlying subendothelial matrix is exposed, initiating the first stage of tissue repair, characterized by hemostasis and the formation of a matrix in the wound bed. This matrix is the result of the adhesion and aggregation of circulating platelets to the components of the underlying ECM. Damaged tissue and aggregated platelets trigger extrinsic and intrinsic coagulation pathways to stabilize the fibrin platelet

clot. This whole process forms a framework for the migration and proliferation of other cells involved in wound healing, as well as a reservoir for cytokines and growth factors [8].

The inflammatory phase then begins as an innate immune response to promote the elimination of cellular and extracellular debris as well as pathogenic microorganisms. Both platelets and leukocytes release inflammatory cytokines providing a chemotactic gradient for additional leukocytes to be attracted and potentiate the inflammatory process. Among the inflammatory factors are interleukin IL-1α, IL-1β, IL-6, IL-8, tumor necrosis factor (TNF-α), platelet-derived growth factor (PDGF) and transforming growth factor-β. Clearly, PDGF plays an important role early in the chemotaxis of neutrophils, monocytes, smooth muscle cells and fibroblasts, while TGF-β stimulates cytokine secretion from macrophages and enhances chemotaxis of fibroblasts and smooth muscle cells [9].

The initial leukocyte response is dominated by neutrophils in the first 2–5 days, with macrophages taking over from the third day. Neutrophils have three main functions. First, they generate free radicals via the myeloperoxidase pathway to kill bacteria, an important action for healing because wounds that have bacterial infection will not heal normally. They also debride the wound through the secretion of specific proteolytic enzymes that break non-viable tissue, such as serine proteases and matrix metalloproteinase (MMP-2 and -9). Hence, the neutrophils phagocyte the dead bacteria and the remained matrix. They usually undergo apoptosis when their tasks are completed and are cleansed by macrophages [9, 10].

The monocytes begin to migrate to the wound and mature into macrophages. They become the most important regulatory cell in the inflammatory reaction. In the early stages of inflammation, M1 phenotype macrophages are associated with the phagocytic activity of remaining bacteria, sequestration and production of pro-inflammatory mediators. After this period, M1 becomes the subset M2, revealing a reparative phenotype of macrophages [1]. M2 macrophages are involved in the synthesis of anti-inflammatory mediators and tissue cleansing. These cells remove obsolete neutrophils, non-functional host cells, damaged matrix, and foreign debris. M2 cells also secrete various cytokines, growth factors and other mediators, such as TGF-α, TGF-β, basic fibroblast growth factor (β-FGF), PDGF and vascular endothelial growth factor (VEGF) to amplify and resolve inflammation. At this stage of healing, macrophages regulate the proliferative stage by stimulating fibroblasts, keratinocytes and endothelial cells to differentiate, proliferate and migrate, leading to new ECM deposition, re-epithelialization and wound neovascularization [11].

The goal of the proliferative stage is to decrease the area of contracted tissue and fibroplasia, establishing a viable epithelial barrier to activate keratinocytes. TGF-β stimulated fibroblasts differentiate into myofibroblasts rich in alpha smooth muscle actin and can amplify pseudopodia, joining fibronectin and collagen in the ECM. This event provides wound contraction, which is important in the repair process, helping the edges of the wound approach. These cells are also producers of ECM substances (collagen, fibronectin, glycosaminoglycans, proteoglycans and hyaluronic acid), which interact with the cells to mediate migration, growth and differentiation. This stage is characterized by the lesion closure, which includes angiogenesis, fibroplasia and re-epithelialization [7, 12].

The final stage of wound healing is characterized by the development of new epithelium and formation of scar tissue, a process known as remodeling, which can last for a year or stay for a longer period. The main purpose of the remodeling step is to achieve maximum tensile strength through reorganization, degradation and resynthesis of ECM. Together with intracellular matrix maturation, collagen bundles increase in diameter, whereas hyaluronic acid and fibronectin are degraded. The force of traction of the wound progressively increases with the deposition of

collagen, and these fibers can recover approximately 80% of the force compared to normal tissue, but the force of the original tissue can never be recovered again [12].

As demonstrated, many factors can alter positively or negatively the cell interactions and the signaling mechanisms during the wound healing process. Plant-derived compounds are among these factors and are able to improve the healing process through different mechanisms.

3. Plant-derived compounds

Medicinal plants have been extensively used worldwide as traditional treatment for various diseases due to being a source of phytochemicals, which are nonnutritive substances present in plants enhancing tissue regeneration and acting as pro-angiogenic agents for wound healing. In addition, bioactive products extracted from plants arouse scientific and commercial interests for the development of new drugs [13]. On the other hand, plants are also source of many macromolecules such as carbohydrate and proteins extensively used as biomaterials for wound healing applications.

3.1 Essential oils

Essential oils (EOs) are the largest group of secondary metabolites biosynthesized by plant as a complex of monoterpenes (10 carbons) and sesquiterpenes (15 carbons), mainly related to plant defense mechanisms. Also known as volatile oils or aromatic plant essences, they can be found in a multitude of plant tissues such as flowers, leaves, barks, etc. Obtained by aqueous extraction or steam distillation, or cold pressing in the case of citric fruits, they have been extensively employed in cosmeceuticals and dermaceutical products [14, 15].

In the healing process, the OEs stand out for their anti-inflammatory and antimicrobial properties. The efficacy in inhibiting bacterial development, including antibiotic-resistant strains, yeasts and filamentous fungi, has boosted the study of the antimicrobial activity of essential oils. Some oils extracted from medicinal plants demonstrated therapeutic potential in combating biofilms, a mechanism of virulence produced by pathogenic microorganisms, resistant to antibiotics [16]. Carvacrol and Thymol, for example, are monoterpenes widely found in essential oils *Origanum* genus, presenting antibacterial and antifungal activities [17] in addition to analgesic effect [18]. In several studies, it has been reported that interactions between the components of EOs, even in small concentrations, may lead to antagonistic, additive or synergistic effects [15].

Although EOs are a mix of plant molecules with many applications such as antimicrobial, anti-inflammatory, besides potential healing properties, as stated above, we draw our attention here to plant polysaccharides and lectins.

3.2 Carbohydrates

Essentially, seeds play an important role in the reproductive strategies of certain species and represent a critical phase in life cycle of plants. Also, they play a vital role in diet and human health, which fosters a wide range of potential applications explored by science and technology. Substantial contributions to human well-being and health have emerged from these applications in fields such as the development of biopharmaceuticals [19].

All cells in higher plants present in their cell wall a complex network formed by numerous polymers including cellulose, non-cellulosic polysaccharides (pectin),

structural glycoproteins and, on the secondary wall, lignin. A singular characteristic of plant cell walls is the presence of cellulose, consisting of glucose chains linked to β-(1→4), organized in microfibrils [20, 21]. Intertwined with these microfibrils, a series of hemicelluloses, which are polysaccharides that have similar characteristics to cellulose, are found crosslinked to it.

3.2.1 Plant cell wall polysaccharides

Cell wall polysaccharides can be divided into structural and storage polysaccharides. Primary and secondary walls contain cellulose and hemicelluloses, pectin in addition to enzymes and structural proteins, while the secondary walls contain few proteins or pectin, but usually contain lignin. Secondary cell walls appear when the cell interrupts its growth and often exhibit elaborate specializations for which the incorporation of lignin is usually the most distinctive characteristic. Therefore, the secondary walls of cotyledonary and endospermic cells in seeds of many species do not have lignin and contain low cellulose [22, 23].

On the other hand, in some seeds, cell wall of storage tissues (endosperm or cotyledon) is quite thick and contains deposits of polysaccharides, which are mobilized after germination. These polysaccharides are called cell wall storage polysaccharides (CWSPs) and are split into: mannans; galactomannans and glucomannans; xyloglucans and galactans [22].

Storage polysaccharides are mostly water soluble and form viscous and stable dispersions, normally absorbing a large amount of this solvent. It assures water around the embryo during the imbibition and germination process, helping protect against dehydration [22].

3.2.1.1 Galactomannans

Galactomannans are neutral cell wall polysaccharides, commonly found in endosperm of dicotyledonous seeds. They perform the storage function, being usually catabolized to provide energy and carbon skeletons to the plant during germination. They are more abundant in seeds of *Leguminosae* family in which the four major sources of commercial importance are locust bean (*Ceratonia siliqua*), guar (*Cyamopsis tetragonoloba*), tara (*Caesalpinia spinosa* Kuntze) and fenugreek (*Trigonella foenum-graecum* L.) [24].

As can be seen in **Figure 1**, galactomannan are heterogeneous polysaccharides presenting a linear chain of D-mannopyranose residues linked by β-glycoside bonds (1→4) with D-galactopyranosyl attached to these via α-type glycosidic bonds (1→6). In spite of this structure, galactomannans are also called hemicelluloses,

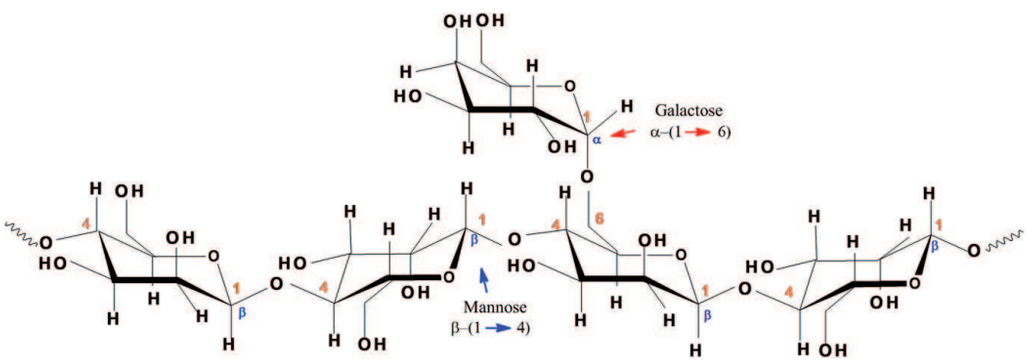

Figure 1.
General structure of galactomannan, considered a hemicellulose by sharing the equatorial β-(1→4)-linked backbone with cellulose. Galactosyl residues are attached to the main backbone by α-glycosyl bonds.

and variations in this Gal/Man ratio cause significant changes in physicochemical parameters such as average molecular weight, intrinsic viscosity and polydispersity of this natural polymers. In addition, the solubility in water is significantly affected by this sugar ratio, which may vary depending of source and isolation procedure. As observed, the higher is the main backbone substituted by galactosyl residues, the more is soluble the galactomannan in water [25].

3.2.1.2 Xyloglucans

Xyloglucans are plant polysaccharides with both structural and storage function, found in the primary cell wall of cotyledon of various seeds. Their main chain consists of D-glucopyranose linked by β-(1→4) and branched in O-6 by α-D-xylopyranoside units, which can also be substituted in O-2 by units of β-D-galactopyranosyl [22]. This group of polysaccharides plays a fundamental role controlling cell expansion. Experimental results evidenced xyloglucans associated with microfibrils, suggesting that like other hemicelluloses, they are able to provide mechanical resistance and physical integrity to the complex arrangements in plant cell walls [26].

With reference to this association to cellulose, xyloglucans are bound via hydrogen bonds and due to their long polysaccharide chains, they assure the maintenance of network microfibrils in cell wall expansion [22]. **Figure 2** displays the common structure of storage xyloglucans, which make them able to form hydrogels and films solutions to be molded in wound dressings able to carrier potential healing molecules [27].

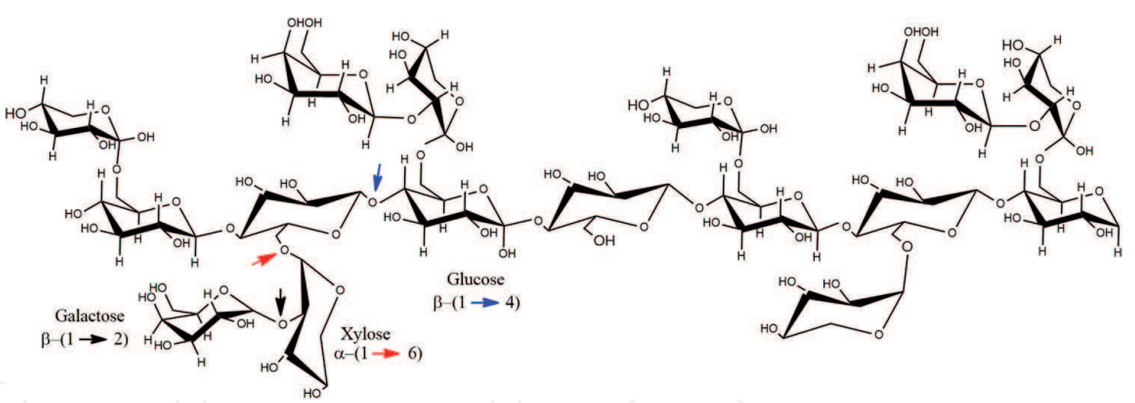

Figure 2.
Xyloglucan structure. As a hemicellulose, they have a backbone composed of β-(1,4)-linked glucans, and conversely to galactomannan structure, xyloglucans present β-(1,2)-linked galactosyl residues. This latter can also be found branched with an α-l-fucosyl residue. However, storage xyloglucan is not fucosylated.

3.2.2 Exudate gums (Arabic, tragacanth and cashew gum)

Exudate gums are hydrocolloids of high molecular weight and viscous appearance, derived from the exudates of branches and bark of the trunks of some plant species. In order to obtain these compounds, a process called gummosis must occur, phenomenon generated as a physiological defense response by chemical, physical and biological stimulus [28]. Chemically, they are made of a complex structure found in arabinogalactans, galacturonans, glucoronomannan or glucoronomannan of acid nature, branched and replaced by major elements (C, H, O and N), inorganic ions and secondary metabolites synthesized from the phenylpropanoid pathway (tannins, terpenoids and other phenolic compounds) [29].

Arabic gum (AG) is a polysaccharide with complex and branched structures (adhesive and cohesive properties) composed of side and main-chains with

β(1,3) and (1,6), respectively, and D-galactopyranosyl, α-L-arabinofuranosyl, α-L-rhamnopyranosyl and β-D-glucopyran units. In some cases, GA is covalently associated with protein fractions and a high content of hydroxyproline, leucine, serine and proline residues [30]. Among its recognized pharmacological properties, we can cite its performance as mucous and intestinal anti-inflammatory, antibacterial and antioxidant, biochemical factors that are probably influential in the wound healing process [31–33].

Tragacanth gum (TG) is an anionic acid branched hetero-polymer with residual units of arabinose, glucose, xylose, galactose rhamnose, fucose and galacturonic acid [32], and TG has important biological characteristics, such as biodegradable and biocompatible biomaterials, resulting in suitable materials in the design of hybrid scaffolds with pharmaceutical applications, *development* of polymeric systems for *controlled release of drug* and guided tissue regeneration [34].

Similar to the polymer gums described above, cashew tree gum is extracted from *Anacardium* genus species, which are abundant Brazilian Northeast. The chemical structure is composed of a main-chain of β-galactose (1–3) and branched-bonds (1–6), containing side-residues of glucuronic acid, 4-O-methyl glucuronic arabinose, rhamnose, xylose, glucose and mannose [32]. The biochemical characteristics associated with biological activities demonstrate anti-inflammatory properties, regulators of oxidative stress and reactive oxygen species, antibacterial and gastroprotective effect [35].

3.3 Proteins

3.3.1 Latex proteases

Latex is produced and stored by laticifer ducts found in some plant species. This fluid is a rich source of natural compounds such as secondary metabolites, glycosides and proteases [36]. Latex proteins have been studied by several researchers as innovative natural compounds for biomedical applications [37]. Among the most common macromolecules from protein origin are cysteine and serine peptidases, also known as latex proteases or latex peptidases. These macromolecules provide the front line of defense against natural enemies in plants acting by synergism with others latex sap proteins [36].

Proteases are also present in animals and humans, and these enzymes have gained notoriety in medical and pharmaceutical field due to their proteolysis functions, specificity and bioactivity [38]. In human biological systems, proteases such as metalloproteinases are endogenously released by fibroblasts, macrophages, mast cells and endothelial cells after injury in extracellular matrix [39]. These enzymes initially participate in the inflammatory phase of healing by debriding the wound necrotic tissue and contributing to collagen remodeling and reduction of scar tensile strength, the later phase of cicatricial process [40]. Proteases and their inhibitors also contribute to degradation and deposition of ECM, creating a balance that is essential for the adequate and coordinated cutaneous wound healing [41].

The modulation of ECM proteases with laticifer proteins has been used as a strategy to improve the performance of healing processes in acute and chronic wounds [42]. Recent advances in plant latex biotechnology has contributed to study the pharmacological properties of proteases-rich fractions from *Calotropis procera* latex revealing its potential role in procoagulation and blood clot hydrolysis [43], modulation of inflammation [44, 45] and enhanced wound healing in animal models using biomembranes of polyvinyl alcohol as vehicle for releasing laticifer proteins [46, 47]. In addition, a phytomodulatory galactomannan-based hydrogel has been successfully used to carrier latex proteases from *C. procera* in experimental

excisional wound models. It was observed a synergic effect between both galactomannan and proteases macromolecules, enhancing the healing [48].

3.3.2 Lectins

Lectins (from Latin "*legere,*" to pick out or choose) are proteins or glycoproteins found in nonimmune nature which can specifically recognize and reversibly bind carbohydrate moieties without altering the covalent structure of their glycosyl ligands. Indeed, this attractive characteristic distinguishes lectins from other carbohydrate binding proteins and enzymes. They are also widely distributed in the plant kingdom, usually from leguminous seed origin and play crucial roles and functions in biological processes such as molecular recognition, storage proteins and plant defense mechanisms. Their interaction with glycosyl ligands occurs mainly through hydrogen bonds, van der Waals' forces, hydrophobic interactions and, less frequently, electrostatic interactions [49]. Here, we emphasize lectins from jackfruit, breadfruit and chempedak (**Figure 3**) and their biological applications.

Lectins were first discovered in plants and, although ubiquitously distributed in nature (animals, insects, viruses, fungi and bacteria), and the majority have been characterized from plant protein extracts, reflecting ease of extraction and relatively high yields usually via a simple one-step affinity chromatographic method [50]. After the discovery of jacalin, novel lectins sharing high homology to it were placed into a family of jacalin-related lectins (JRL), now divided into two different subgroups. The first comprises galactose-specific lectins (gJRL) and a few other Moraceae lectins, which exhibit specificity toward galactose and are built up of subunits consisting of a short β chain and a long α chain. The second is the mannose-binding subgroup (mJRL), which occurs in different plant families with the lectins exhibiting exclusive specificity toward glucose/mannose residues with the binding subunits contained within a single polypeptide chain [51, 52].

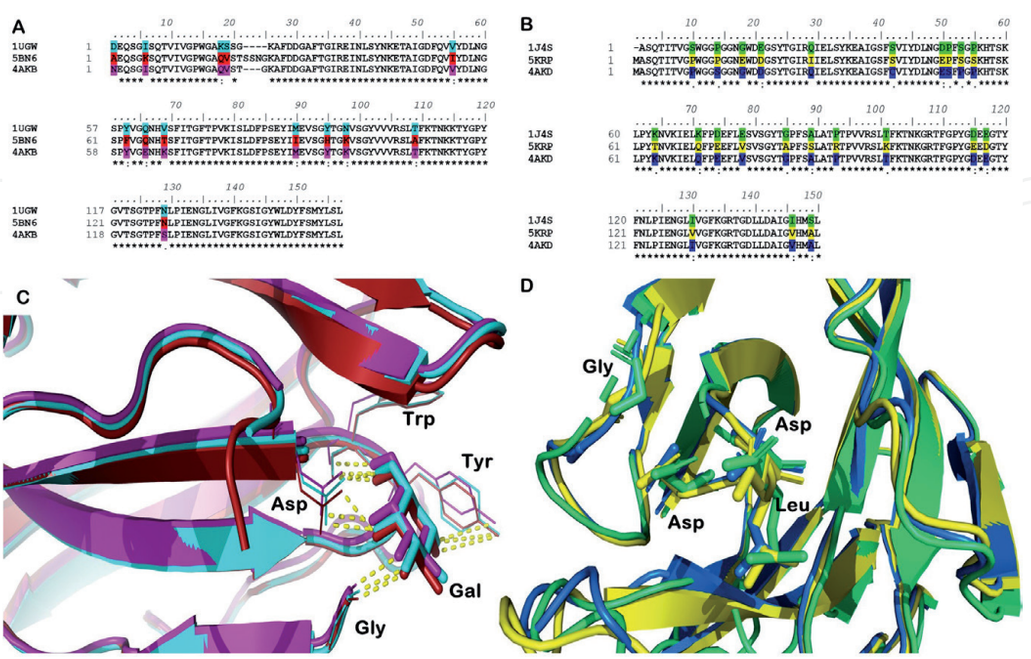

Figure 3.
Artocarpus species. (A) Jackfruit. (B) Cut section of jackfruit. (C) Jackfruit seeds. (D) Breadfruit (var. seminifera). (E) Cut section of breadfruit (var. seminifera). (F) Breadfruit (var. seminifera) seeds. (G) Breadfruit (var. apyrena). (H) Cut section of breadfruit (var. apyrena). (I) Chempedak.

3.3.2.1 Artocarpus lectins

Artocarpus is a genus comprising about 60 trees and shrubs of Southeast Asian and Pacific origin, belonging to the Moraceae family; all species are lactiferous with leaves, twigs, and stems producing milky sap. The name is derived from the Greek words *artos* ("bread") and *karpos* ("fruit"). Although most species of *Artocarpus* are restricted to Southeast Asia, such as *A. hypargyreus* (kwai muk), *A. lakoocha* (lakoocha), *A. kemando* (pudau), *A. hirsutus* (anjily), *A. chama* (chaplaish) and *A. odoratissimus* (marang), several species are widely distributed and cultivated throughout the tropics due to their edible fruits and timber. These include *A. heterophyllus* (jackfruit), *A. altilis* and *A. integer* (cempedak, also known as chempedak) [53–55], well-known species conspicuous as substantial sources of plant lectins which are readily recovered from their seed flour.

3.3.2.1.1 Jackfruit (jacalin, ArtinM and jackin)

The species has an extensive record of use in folk medicine including treatment of asthma, dermatitis, anemia, diarrhea and fever; antisyphilitic and anthelmintic properties; sedative effects in convulsions; and also wound healing properties [56]. Indeed, jackfruit are in high demand in areas such as cosmeceutical, pharmaceutical and natural food handling for supplement markets, due to numerous studies on phytochemical and pharmacological properties of all parts of the plant (pulp, leaf, root and bark) [57, 58].

Extracts and metabolites from jackfruit possess several useful bioactive compounds and may confer multiple health-promoting effects for heart and skin disorders and to treat ulcers and cancer [59]. Moreover, new studies of jackfruit properties provide additional biological findings consistent with antibacterial, antitubercular, antiviral, antifungal, antiplatelet and antiarthritic actions, thereby indicating therapeutic applications [56].

The occurrence of jacalin, the D-galactose-binding lectin from *A. integrifolia* seeds was first reported in 1979 [60] and found to exceed 50% of the protein in jackfruit crude seed extracts. This is also the case for galactose-binding lectins in the *Artocarpus* genus such as frutalin and CGB (chempedak galactose-binding). Jacalin is a tetrameric two-chain lectin of 65 kDa combining a heavy α-chain of 133 amino acids and light β-chain of 20–21 amino acid to form a 3D structure as a single globular unit. By SDS-PAGE, this lectin shows two bands between 20 and 14 kDa, which correspond to glycosylated and slightly or non-glycosylated forms, respectively [61].

The carbohydrate-binding site (CBS) of jacalin mainly involves residues Gly1, Tyr78, Val80, Gly121, Tyr122, Trp123 and Asp125. In D-galactose-jacalin complexes, the O4 hydroxyl group of the galactose axial position forms hydrogen bonds with the side chain of Asp125 and the terminal amino group of Gly1. If O4 is at the equatorial position, as in glucose and mannose, Asp125 can still interact with O4, but not the amino group. This explains the high specificity of jacalin for galactose compared to glucose and mannose at the primary binding site. Additionally, the post-translational cleavage and removal of the "T-S-S-N" peptide linker assure a stronger hydrogen bond connecting the α- and β-chains, as non-cleavage leaves a neutral peptide NH group [62, 63].

Further studies post-discovery of jacalin revealed that jackfruit seed extracts also possess small amounts of a D-mannose-binding lectin [64]. Previously named artocarpin, the term was provisionally replaced by the name KM+; the lectin had become confused with distinct substances from *Artocarpus* spp. which were

similarly designated. Additionally, artocarpin was used to name the galactose-binding lectin in *Artocarpus lakoocha* seeds [65].

The origin of the name KM+ comes from the successive affinity chromatography steps in immobilized D-galactose matrices to remove jacalin (retained fraction J). The unretained fraction was called K, while M+ refers to the retained fraction on immobilized mannose matrices. Nevertheless, there remained confusion over this adopted nomenclature, which led to the proposal for a rational name change to ArtinM based on the universal code for plant proteins. This takes into account both a lectin's origin and specificity of sugar recognition [66]. Hereafter, we will apply ArtinM to include early work and mentions of KM+ (artocarpin).

ArtinM is a single polypeptide of 150 amino acids devoid of covalently attached carbohydrates with four isolectins and a pI range of 5–6.5, sharing 52% sequence identity with jacalin [67]. Unlike jacalin, there are no aromatic residues on the CBS of ArtinM, comprising Gly15, Asp138, Leu139 and Asp141. Indeed, it is believed that the galactose specificity of jacalin was achieved by a two-step process with ArtinM as its putative precursor: mutation of key aliphatic residues close to the sugar binding pocket to aromatic ones; and then cleavage of a short loop, a key step as it creates a positively charged N-terminal which interacts specifically with O4 at the axial position [68, 69].

Besides jacalin and ArtinM, jackfruit seeds are the source of a third lectin named jackin due to its affinity for chitin. Nevertheless, its low yield from natural sources still hampers further characterization, though this might soon be overcome with high-yield heterologous production in microbial systems [70].

3.3.2.1.2 Breadfruit

The Pacific Islands are the center of origin and diversity of breadfruit (*A. altilis*), sometimes referred to as *A. communis* or *A. incisa*. The species was derived from a seeded, diploid ancestor, *A. camansi,* giving two varieties, one seeded (var. seminifera) whose rind spines are as prominent as those on jackfruit, and one seedless (var. apyrena), which presents a spineless outer layer. The latter is well-appreciated by local Brazilians when cooked, because of its large starchy content of compound fruits with high levels of minerals and provitamin A carotenoids [53, 55, 71]. Breadfruit flour was approved in 2016 by the US Food and Drug Administration (FDA) as a food Generally Recognized as Safe (GRAS).

As of 1983, our group started to survey lectins in *A. incisa* seeds and found lectins with similar behavior to those in jackfruit seeds [72]. Breadfruit seeds are composed of a high-water content (up to 60%) and moderate protein content (12.25% of dry weight). Most of this protein is recovered as frutalin in chromatographic methods using crude extracts of seed flour. Therefore, frutalin is the most abundant lectin of this species, presenting multiple-binding properties in which the same CBS recognizes a range of different ligands, although it has higher affinities for α-D-galactose monosaccharides and complex carbohydrates that contain Galα1–3 glycans [73].

The CBS of frutalin in the binding of galactose is dominated by hydrogen bonding through O1, O3, O5 and O6 and backbone/side chain hydroxyl groups. Similar to the Moraceae lectins, the CBS of frutalin is located in a domain close to the N-terminus of the α chain, consisting of four key residues Gly25, Tyr146, Trp147 and Asp149. About 10 interactions occur, involving the C1 hydroxyl to residue Tyr146, hydroxyl C3 to residue Gly25, hydroxyl C4 to residues Gly25 and Asp149, and hydroxyl C6 to residues Tyr146, Trp147 and Asp149 [74]. Moreover, there is evidence to suggest that frutalin possesses stereospecificity, capable of specifically

binding α-D-galactose, since it was previously isolated on a cross-linked galactomannan column, but not on β-galactosyl-immobilized matrices [73, 75].

Frutapin (FTP) is the next most abundant lectin in breadfruit seed extracts. Preliminary, FTP investigations began in 1998, describing three different lectins with distinct carbohydrate recognition within the same species [76]. However, further studies proved difficult since native FTP was hampered by very low yields and contamination with Frutalin, a notable factor as frutalin binds diverse sugar moieties and has high abundance in plant extracts. Recombinant FTP production is now a feasible approach to circumvent this problem, allowing large-scale heterologous expression to give continuous supplies for further characterization and to improve potency, particularly for biomedical applications [77].

FTP is a hololectin defined as a homotetramer with an identical CBS per protomer, able to bind either the same or structurally similar sugars. The CBS is formed of four residues, namely Gly16, Asp139, Leu140 and Asp142, distributed in a few loops connecting the strands β5 and β6, β7 and β8, and β11 and β12. Several hydrogen bonds (HB) occur in FTP-glucose and FTP-mannose complexes involving Gly16, Leu90, Gly138, Asp139, Leu140, Asp142 and O3, O4, O5, O6 of the carbohydrates. In MD simulations, Lys60 plays an important role forming salt bridges with Asp139 in FTP-glucose complexes, reducing the interaction between this former residue and mannose and minimizing the repulsion of the mannose hydroxyl groups with oxygen. In this case, mannose was more completely surrounded in the carbohydrate-binding site and also stabilized by indirect interaction with Asp139 through water molecules. This local structuring is more stable in the case of mannose than glucose, indicating a higher affinity of FTP for mannose residues than glucose [78].

Further studies of breadfruit seeds also revealed a lectin similar to jackin, named frutackin. Both lectins have a 14 kDa polypeptide chain, built up of three chains linked by disulfide bonds, the partial amino acid sequences of the two lectins showing their homology to each other in terms of molecular mass, secondary structure, and primary sequence, but not to other plant chitin-binding proteins. Both jackin and frutackin inhibit the growth of *F. moniliforme* and *S. cerevisiae* [70].

3.3.2.1.3 Chempedak

Although widely known in the tropics as chempedak or chempedak, *Artocarpus integer* (Thumb.) Merr. is native to India with similar fruits to jackfruit. The *A. integer* species is rich in phenolic compounds, presenting a strong cytotoxic activity against murine leukemia P-388 [79]. Moreover, a chempedak paste of the inner bark prevents infection and helps healing when applied on wounds, as well as heated leaf extract [80].

Chempedak galactose-binding lectin (CGB) is found in high levels *A. integer* seed flour extracts. The lectin's bioactivity was first noted when extracts were tested for selective stimulation of peripheral blood mononuclear cells; at 20 μg/mL CGB stimulated proliferation of T-lymphocyte populations [81, 82]. Like frutalin and jacalin, CGB is transcribed as a propeptide and then post-translationally processed into a typical gJRL lectin, having a 13-kDa α-chain (133 amino acids) and a 2.1-kDa β-chain (21 amino acids). CGB has six different amino-acids compared to jacalin, giving 97% identity for their amino-acid sequences [83].

As with jacalin complexes, the interactions are well conserved, presenting the same CBS. In Gal-CGB complexes, the O atoms on the sugar ring are bound with the side-chain and main-chain N and O atoms on the α chain (O3 and Gly1 N; O4 and Gly1 N and Asp125 OD1; O6 and Trp123 O, Trp123 N and Tyr122 N; and O5 and Tyr122 N). Similarly, GalNac-CGB complexes present bound disaccharide in the same region though hydrogen bonds (O3 and Gly1 N; O4 and Gly1 N and Asp125 OD1; and O6

and Asp125 OD1). Also, there are a number of hydrophobic interactions contributed by Tyr78, Gly121 and Tyr122. Although closely related to jacalin's structure, CGB was unable to bind mannose as judged by isothermal calorimetry and co-crystallization studies. It is believed that this change in CGB specificity is caused by subtle differences in the environment near the sugar-binding site, including solvent molecules.

Extracts of *Artocarpus integer* seeds are a source of CMB, previously termed chempedak lectin-M [84]. The lectin is ~20-fold more abundant than ArtinM in crude extracts of *A. heterophyllus* seeds. Structural studies reveal CMB to be a 64-kDa tetramer with some of the polypeptides being disulfide-linked to give dimers. The functional activity of CMB was assessed by studying interactions with different isotypes of human immunoglobulins: strong binding to IgE and IgM was noted, unlike CGB and jacalin which strongly interact with IgA1. The lectin also shows a similar pattern of carbohydrate binding specificity to ArtinM with Man-α-1–3Man the most potent inhibitor, followed by methyl-α-D-mannopyranose and D-mannose [84].

It appears that the *Artocarpus* genus employs a plurality of lectins, though to date few of these lectins have been purified and functionally characterized. Nevertheless, a consistent pattern is that *Artocarpus* seeds contain more than one lectin with distinct carbohydrate recognition features [70, 76]. Altogether, the JRL family is complex with a vast diversity in biochemical properties and activities, which have drawn much attention because of their pivotal biomedical applications. Owing to carbohydrate-binding interactions of plant lectins with cell wall glycoproteins, they are promising targets to selectively modulate immune responses in plants. Hence, it is important to delineate the molecular details of lectin binding to CBS domains and how downstream activation of cellular immune signaling proceeds [85]. In this context, it is of particular note that *Artocarpus* lectins have a distinct repertoire of biological activities, despite their high sequence and structural homology, as can be seen in **Figure 4**.

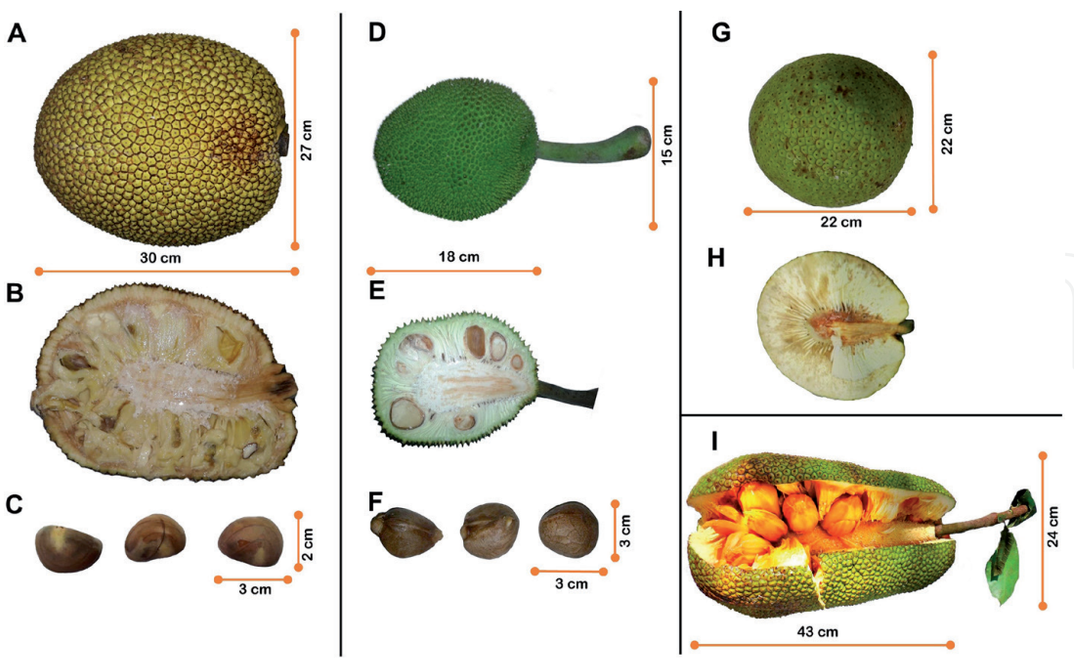

Figure 4.
Sequence alignment using Clustal W and structural superposition of Artocarpus *lectins. (A) Sequence alignment of galactose-binding lectins: Jacalin (PDB 1UGW), Frutalin (PDB 5BN6), and CGB (PDB 4AKB). (B) Sequence alignment of mannose-binding lectins: ArtinM (PDB 1J4S), frutapin (PDB 5KRP) and CMB (PDB 4AKD). (C) Structural superposition of galactose-binding lectins with their carbohydrate interacting residues in complex with D-galactose: jacalin (cyan), frutalin (red) and CGB (magenta). (D) Structural superposition of mannose-binding lectins with the carbohydrate interacting residues highlighted: ArtinM (green), frutapin (yellow) and CMB (blue).*

4. Recent advances using plant biomaterials for wound healing

The worldwide increasing number of chronic-wound patients has driven an intense effort in the wound-care market in search of low cost and effective wound healing technologies [86]. Therefore, much of this knowledge is eligible for patents that play an important role in identifying technology development trends [86].

In the following table, we highlight the main efforts in the last 5 years on the development of biomaterials using plant macromolecules as source of biomolecules with potential for wound healing applications (**Table 1**).

Title	Plant biomaterial	Description	IPC code	Ref.
Necrotic tissue composition remover for wound healing	Protease mixture	An aqueous gel is carrier for a protease mixture for removing necrotic tissue in chronic wounds.	A61K38/4873	[87]
Compound preparation for wound healing and postpartum rehabilitation	Hydrolysate: synthases I, alkaline protease and papain	Compound preparations that promote blood circulation and wound healing.	A61K 36/00	[88]
Dead Sea Water and apple of Sodom extract compositions and uses thereof	*C. procera*	The compositions may be used for topical administration in wound healing.	—	[89]
Therapeutic composition for wound healing	β-glucan and at least one secondary polysaccharide group consisting of arabinogalactan, fucoidan, pectin and galactomannan	Therapeutic composition as a potent stimulator for wound healing.	A61K 31/716	[90]
Anti-adhesion material with antibacterial and healing properties	Xyloglucan	The material is used for preventing reoccurrence of adhesion after adhesion loss operation, and meanwhile has functions of preventing bacteria and promoting wound healing.	A61L31/041	[91]
Plant hemicelluloses and lectins formulations with healing activity	Hemicelluloses and plant lectins	Hydrogels and biomembranes are used to treat wounds, abrasions, burns, varicose ulcers, decubitus ulcers, open superficial wounds with or without infection.	A61K 31/736	[92]

IPC: International Patent Classification.

Table 1.
Recent patents of plant biomaterials for wound healing.

5. Conclusion

As an orchestrated sequence of biochemical and cellular events for tissue repair, the healing process becomes a challenging in a way to develop a universal dressing, attending all the sorts of wound and lesions. It is here that biomaterials are notably relevant for biomedical applications once multiple properties of them can be combined in formulations of new treatments strategies of wound healing and repair. Many plants have been used traditionally in therapeutic treatments of lesions, which make them a remarkable source of biomolecules to wound-care market.

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