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The Therapeutic Potential of Bioactive Polysaccharides in Tissue Repairing and Wound Healing

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ABSTRACT

The process of wound healing is highly complex, and any changes of the key healing factors or components can produce undesirable outcomes. Current clinical practices such as off-loading, debridement, irrigation, suturing, negative therapy of pressure, grafting and the supplementation of growth factors and so on, have limits in addressing the problems of comprehensive wound care. Due to the dynamic nature of the healing process, the best prevention strategies possible are effective wound management in the early stages and preventing the development of wounds to chronic conditions. The immune system has been shown to play a vital role in the physiological process of wound healing and tissue repair. Many agents that affect the immune system positively, both synthetic and natural, were shown to have implications for wound healing process. In particular, bioactive materials have shown promising consequences in this area, as a result of advances in inter-disciplinary approaches that can potentially be used as a smart wound care. Natural polysaccharides, with their clearly elucidated structures, identified cellular activities and desirable physical properties have the potential to work as therapeutic tools for tissue regeneration and wound healing. In this review article we discuss briefly the essential role of the immune system and emergence of natural wound healing polysaccharide applications. First, we introduce natural polysaccharides and their biological activities from natural sources. Then, we discuss some natural polysaccharides with growth factor-binding affinities and inspired polymer tools, focusing on how wound-healing and tissue reparation can possibly benefit from these promising polysaccharides.

Keywords: Natural, polysaccharides, wound, healing, regeneration, tissue, repair, therapy

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INTRODUCTION

Wound is an increasing challenge for healthcare affecting several million people around the world. Disorders like diabetes, which affect lifestyle, can increase the risk of injury complications. The complications caused by co-morbidities such as infections or diabetes makes the wound one of the main health concerns. World Health Organization (WHO, 2014) statistics indicated that 58 million people suffer fatal injuries, of whom 5 million die per year and several million remaining people need proper care and treatment. Although over 3000 products were designed for the treatment of wounds and for tissue repairing, the social and individual burdens remain (Dhivya *et al.,* 2015).

The wound-healing process is highly complex, and any changes of the key healing factors or components can produce undesirable outcomes (Figure 1), therefore, it is still a burden and rather a complicated process (Guo 2010; Anderson 2012; Jarbrink *et al.,* 2017). Current clinical practices such as offloading, debridement, irrigation, suturing, negative therapy of pressure, grafting and the supplementation of growth factors etc. have limits in addressing the problems of comprehensive wound care (Sarabahi, 2012). Wound healing process is not only complex but also dynamic, involving a cascade of biological injury reactions (Figure 1). We and others have shown that, the interaction of immune cells (neutrophils, monocytes, macrophages, lymphocytes); non-immune cells (endothelial, fibroblasts, keratinocyte cells), soluble mediators (cytokines and growth factors) and extra cellular components (ECM) are significant factors for wound healing process (Al'Qteishat *et al.,* 2006; Gurtner *et al.,* 2008).

The rate of healing for acute wounds is different from those for chronic diseases and also depends on the patient's immune status (Demidova-Rice *et al.,* 2012). The involvement of four major overlapping phases, haemostasis, inflammation, proliferation and remodelling, heal wounds in normal conditions. Wounds are cured by primary intention or primary closure, secondary wound healing or spontaneous curing, third intention or delayed primary closure, depending upon the depth and extent of the tissue damage. The methods of treatment are generally based on the type of wound but poor management results in fibrosis, chronic wounds and tissue loss or even amputation (Enoch, 2006). Due to the dynamic nature of the healing process, the best prevention strategies possible are effective wound management in the early stages and preventing the development of wounds to chronic conditions.

The role of immune cells in the process of wound healing

It is well known that the immune system plays an essential role in the process of wound healing and due to the fact that neutrophils, macrophages, and lymphocytes migrate into the wound area, the role of these immune cells and their involvement in wound healing, apart from their role in inflammation has been suspected long time ago (Strbo & Stojadinovic, 2014). The exact role played by these immune cells is not yet fully elucidated, although, it is clear that these cells play important role in wound healing process. Immune cells are essential to regulate the process of wound healing; this could be through the secretion of different proteins, including growth factors and cytokines (Strbo & Stojadinovic, 2014).

The cellular arm of the immune system is known to play an integral role in wound healing process. In addition to performing their regular duties in fighting infection, macrophages and lymphocytes are important in regulating the complex series of events that lead to wound healing (Strbo & Stojadinovic, 2014). Perturbation in the host immune system can manifest as complications in wound healing, as seen in patients with immunosuppression, steroid use, or malnutrition (Tatara *et al.,* 2018; Al-Jabri *et al.,* 2013). A better understanding of the regulatory parameters of wound healing could lead to possible clinical application to decrease the incidence of wound complications or to help heal chronic, and difficult to heal wounds. It is also well known that a healthy immune system and the clearance of infection in a wound will definitely enhance the healing process of the wound.

Apart from having a healthy immune system, scientists have focused on developing therapies for a foetal-like healing process without incidents (Dickinson and Gerecht*,* 2016). Bioactive materials have shown promising consequences in this area, as a result of advances in inter-disciplinary approaches, that can potentially be used as smart wound care (Dickinson and Gerecht*,* 2016).

Moreover, certain polysaccharides have attracted growing scientific interest for their ability to exert marked effects on immune system function, inflammation and cancer (Pelley &, Strickland, 2000). Literature suggests that certain polysaccharides affect immune system function positively. For example, Glucan extracts from the *Trametes versicolor* mushroom improved survival and immune function in patients with cancer (Pelley &, Strickland, 2000). Glucans, arabinogalactans and fucoidans elicited immunomodulatory effects in controlled studies of healthy adults and patients with canker sores and seasonal allergies (Ramberg *et al.,* 2010). Therefore, the positive role of polysaccharides in wound healing and tissue repair is anticipated.

Bioactive polysaccharides and wound healing

The complexity of the healing process often makes effective injury management difficult. The bioactive polymers become ever more important in wound care, in addition to traditional wound treatment practices. Naturally, biopolymers are biomolecules synthesized with highest biocompatibility by microbes, plant and animals (Table 1). A microenvironment favourable for healing is created by the bioactive properties such as the antimicrobial, immune-modulative, proliferative and angiogenic polymers properties (Dhivya *et al.,* 2015).

Many synthetic polymers have been created with well-defined mechanical and degrading properties to meet the technological requirements of biomedical applications (Tian, *et al.,* 2012; Domb and Kumar, 2011; Verma, *et al.,* 2011; Shelke, *et al.,* 2011). Synthetic polymeric lacks the bioactivity or biocompatibility that they require much, and can cause toxicity, inflammation and an immune response to them (Yao, *et al.,* 2011). Much effort is made to improve synthetic bioactivity, by combining it with other natural polymers, proteins and synthetic peptides (Oh & Lee, 2013). On the other hand, the hydroxyl, carboxylic and amine structures are free and enable the alteration of the physicochemical properties of polymers with chemical modification of the structure of polysaccharide (Baldwin & Kiick, 2010).

Natural polysaccharides from different sources, such as food, medications and pharmaceutics, as well as paper production, have long been studied and widely used. In recent decades, there has been an increase in interest in the utilization, due to its biocompatibility, biodegradability of, non-toxicity and certain specific therapeutic activities, of polysaccharides, particularly bioactive applications. There is now decent documented therapeutic potential of natural bioactive compounds, such as polysaccharides, and these activities, together with natural biodiversity, will allow a new generation of therapeutics to emerge.

The major bio-macromolecules are the carbohydrates, along with proteins, lipids and nucleic acids. In most of the carbohydrates found in nature, the monosaccharaides (Aachary & Prapulla, 2011) are found in almost all kingdoms of life, such as algae (for example, alginate) (Rinaudo, 2014), plants (for example, starch and cellulose) (Schepetkin & Quinn, 2006), microbes (for instance, zymosan and dextran) (Yang, & Zhang, 2009) and animals (e.g. hyaluronic acid and heparin) (Zhao, *et al.,* 2015).

Cationic polysaccharides (Chitin, Chitosan) (Yudovin-Farber, *et al.,* 2005), anionic polysaccharides (Heparin, Hyaluronic Acid, Alginic and Chondroitin sulfates) (Xiao, *et al.,* 2011; Funami, *et al.,* 2008), and Non-ionic (Dextrane, Starch, and Cellulose) (Dalheim, *et al.,* 2016) as polysaccharides may also be classified according to their electrical charge.

A glycosaminoglycan in the skin is hyaluronic acid. This is a mammalian biopolymer that is evolutionarily preserved. A high molecular weight compound (5 x10^6 Da) has been found in hyaluronic acid. High molecular weight of hyaluronan is anti-inflammatory in nature, and hyaluronan is pro-inflammative (Litwiniuk, *et al.,* 2016) for the fragments / low molecular weight. The treatment of wounds by inducing fibroblast proliferation, ECM restoration and keratinocyte migration plays a significant role in this wound healing process. We and others have demonstrated that the pro-angiogenic effect is found in the degradation product of hyaluronic acid (Issa R *et al.,* 2005; Al'Qteishat *et al.,* 2006; Al Qteishat *et al.,* 2006) (Figure 2). It triggers a number of cascades by binding the keratinocytes to the CD44 receptors (Al'Qteishat, *et al.,* 2005; Price, *et al.,* 2005). Hyaluronic acid, though an endogenous biopolymer, was shown to modify the curing trend with decreased collagen synthesis by supplementing exogenous hyaluronic acid after injury (Prosdocimi, 2012). Hyaluronan has been effective therapy for tissue repair from this beneficial perspective. A research by Li *et al.,* (2018) found that hyaluronic acid grafted with pullulan has enhanced the anti-enzymes degradation. This was also demonstrated accelerated hemostatic ability healing. Alginates establish a moist environment and accumulate exudates in the wound bed. The wound pain decreases, the risk of wound infection is reduced, the smell reduces, and haemostasis improves. The ion exchange between the calcium ions in the alginate and the sodium ions in the blood or exudates is caused by an alginate containing dressing in wound exudate. The alginate fibres swell, dissolve and form a gel when sufficiently calcium ions have been replaced by sodium ions (Jones, *et al.,* 2006). Murakami *et al.,* (2010) reported the re-epithelialization of mitomycin by the blend of chitosan, alginate and fucoidan treated impaired wound. Several related studies indicated that alginate is feasible for modifications. Embedded alginate of curcumin or silver nanoparticle; composite and chitosan alginate dressings of silk fibroin and alginate have been reported to achieve better healing outcomes (Li, *et al.,* 2012; Wang, *et al.,* 2002; Roh, *et al.,* 2006).

Polysaccharides can also be described as homo-polysaccharide (Korakli & Vogel, 2006) in terms of chemical composition, containing a single monosaccharide type and hetero-polysaccharide (Amid & Mirhosseini, 2012) that contain two or more different monosaccharide types. For example, cellulose consists of unique glucose and heparin consist of α-Idopyranosyluron acid 2-sulfate and 2-deoxy-2-sulfoamino-α-D-glucopyranose 6-sulfate.

Polysaccharides exist in the form of proteoglycans, glycolipids, and glycoconjugates based on different glycosides associated with glycan. The rapid development of bioanalytical technology has made it possible to understand the structure and functions of polysaccharides. In addition to being a building block of life, polysaccharides together with oligosaccharides also provide for numerous biological signals like cell-cell communication, immune recognition (González-Fernández, *et al.,* 2008) and Mitogenesis (Kumbar, *et al.,* 2011).

Biomedical application of bioactive materials

By direct cell interaction or by extracellular matrix mediation, bioactive material can target inflammatory, proliferative or re-model phases of healing. They modulate the pathways of cellular signalling to trigger the growth, differentiation and functioning of key healing agents, such as fibroblasts, keratinocytes, endothelial cells and macrophages. The bioactive materials commonly use biopolymers of various sources. Due to their excellent biocompatibility, abilities to promote cell growth, regenerative capacity, biodegradability and durability, the use of biopolymers as wound care material is highly promising (Eming, *et al.,* 2007; Stramer, *et al.,* 2007).

Polysaccharides application in tissue engineering

Polysaccharides and their derivatives are used for application in the tissue engineering, such as biological signalling, cellular adhesion, cells proliferation, degradation of cells and remodelling. This can attract great attention in medical research to guide, promote and define the shape and structure of cell growth (Khan & Ahmad, 2013). Various polysaccharides have been developed as biomaterial for tissue engineering applications, including alginate, chitin, chitosan, hyaluronic acid, cellulose, chondroitin sulphate, starch and their derivatives (Oliveira & Reis, 2011). (Figures 3 & 6).

Application of polysaccharides as tissue engineering scaffolds requires that they meet requirements such as biocompatibility and non-toxicity, biodegradability and controllable degradation rate, suitable porosity and structural integrity (Khan & Ahmad, 2013). With respect to degradability, immunogenicity and mechanical strength Chitin and Chitosan have all the necessary qualities to function as scaffolds for tissue engineering and have consequently been developed for applications in the fields of tissue engineering in the form of 3D hydrogels or porous sponges, fibrous scaffolds or standing films for in vitro or in vivo culture and evaluation of cell types (Wan & Tai, 2013). The 3D chitin / chitosan hydrogel, sponge scaffold or two-dimensional scaffolds and free-standing films have been recently reported and examined in favour of cartilage regeneration, for chemical interactions with appetite for regeneration of bones and tendons, for encapsulation and differentiation of stem cells and for their growth and differentiation in in regenerative medicine (Croisier & Jérôme, 2013; Lu, *et al.,* 2012; Suh & Matthew, 2000; Wu & Hochedlinger, 2011). In addition, composites of chitosan with hydroxyapatite and grafted chitosan with carbon Nanotubes were developed as potential materials for artificial tissue engineering in artificial bone and bone regeneration (Venkatesan & Kim, 2010). For applications in bone, cartilage and/or skin tissue engineering (Rinaudo, 2008), other polysaccharide- based materials, such as hyaluronic acid, starch and cellulose have also been explored (Figure 6).

Polysaccharides application in tissue repairs and wound healing

Various polysaccharides, such as chitins, chitosan, celluloses, hyaluronan and alginates, have been widely utilized for wound healing materials preparation because of their inherent biocompatibility, low toxicities or pharmaceutical bio-medical activity (Barud Hda *et al.,* 2013; Czaja, *et al.,* 2006; Czaja, *et al.,* 2007; Hrynyk, *et al.,* 2012). For example, and from our own experience, hyaluronan has been extensively developed for tissue reparation due to its physicochemical properties, special interactions with cells, extra-cellular matrix (Al'Qteishat *et al.,* 2006). This is the primary extracellular component with its hygroscopic, rheological, and viscoelastic properties. In all stages of wounds' healing, i.e., inflammation, granulation of tissue formation, re-epithelialization or remodelling, hyaluron is widely recognized as having several facets in the mediation of the tissue repair process (Al'Qteishat *et al.,* 2006). Hyaluronan derivatives have also been developed, for tissue repair or wound healing, as cross-related, esterified or other chemically modified products (Anilkumar, *et al.,* 2011; Chen & Abatangelo, 1999). Moreover, in the development of materials for tissue engineering, wound healing promotes the activity of such materials.

All-natural composite wound dressing films prepared by dispersion and encapsulation of essential oils (elicriso italico, chamomile blue, cinnamon, lavender, tea tree, peppermint, eucalyptus, lemongrass, and lemon oils) in sodium alginate matrices have been reported to show remarkable antimicrobial and anti-fungal properties and may find application as disposable wound dressings (Liakos *et al.,* 2013). Chitosan / silk fibroin blending membranes cross-linked with di-aldehyde alginate have been developed for wound dressing and the membranes were found to promote the cell attachment and proliferation, which suggests a promising candidate for wound healing applications (Gu *et al.,* 2013).

The development of Nano-curcumin / N, O-carboxymethyl chitosan / oxidized alginat hydrogel as a promising wound dressing may potentially be used in wound healing *in vitro* releases, *in vivo* wound healing, and histology studies. The gamma-based synthesis of silver Nanoparticles that contain polyvinyl pyrrolidone and alginate hydrogels showed the ability to protect the fluid accumulation in a tiny wound from exudation (Singh & Singh 2012).

The integration of Nano-silvers had a strong antimicrobial impact, which made these hydrogels suitable for use as wound dressing polyvinyl pyrrolidone and alginate. Other natural polysaccharide products such as cellulose, chitin, chitosan and hyaluronic acid (Anisha, *et al.,* 2013, Kondo, *et al.,* 2012, Matsumoto & Kuroyanagi 2010) have also been exploited, with the exception of alginates and its various derivatives, for wound dressing or wound healing applications.

Conclusion and future aspects of the use of natural polymers

In ECM components of organisms, a majority of the natural polymers participate in and contribute to intercellular and intracellular cellular signalling. Through their implantation in the body, these polymers have a biological identity and thus cannot generate inflammation or immune responses. Natural polymers have many advantages, such as their natural abundance, their relative ease of isolation and their room for chemical changes to meet different technical requirements. Moreover, in the biological environment these polymers are degraded into non-toxic products by enzymes and/or hydrolytes.

Although polysaccharides have many advantages as biomaterials, there are several disadvantages, which have limited the use of polysaccharides in biomedical applications. Many of these polysaccharides, including mechanical stability, degradation and bioactivity, have been chemically modified in order to achieve consistent physicochemical properties and are processed into porous tissue regeneration structures in micro-particles, hydrogels and three-dimensions. The presence of several features on the polymer backbone enables simple changes in structure for the required application.

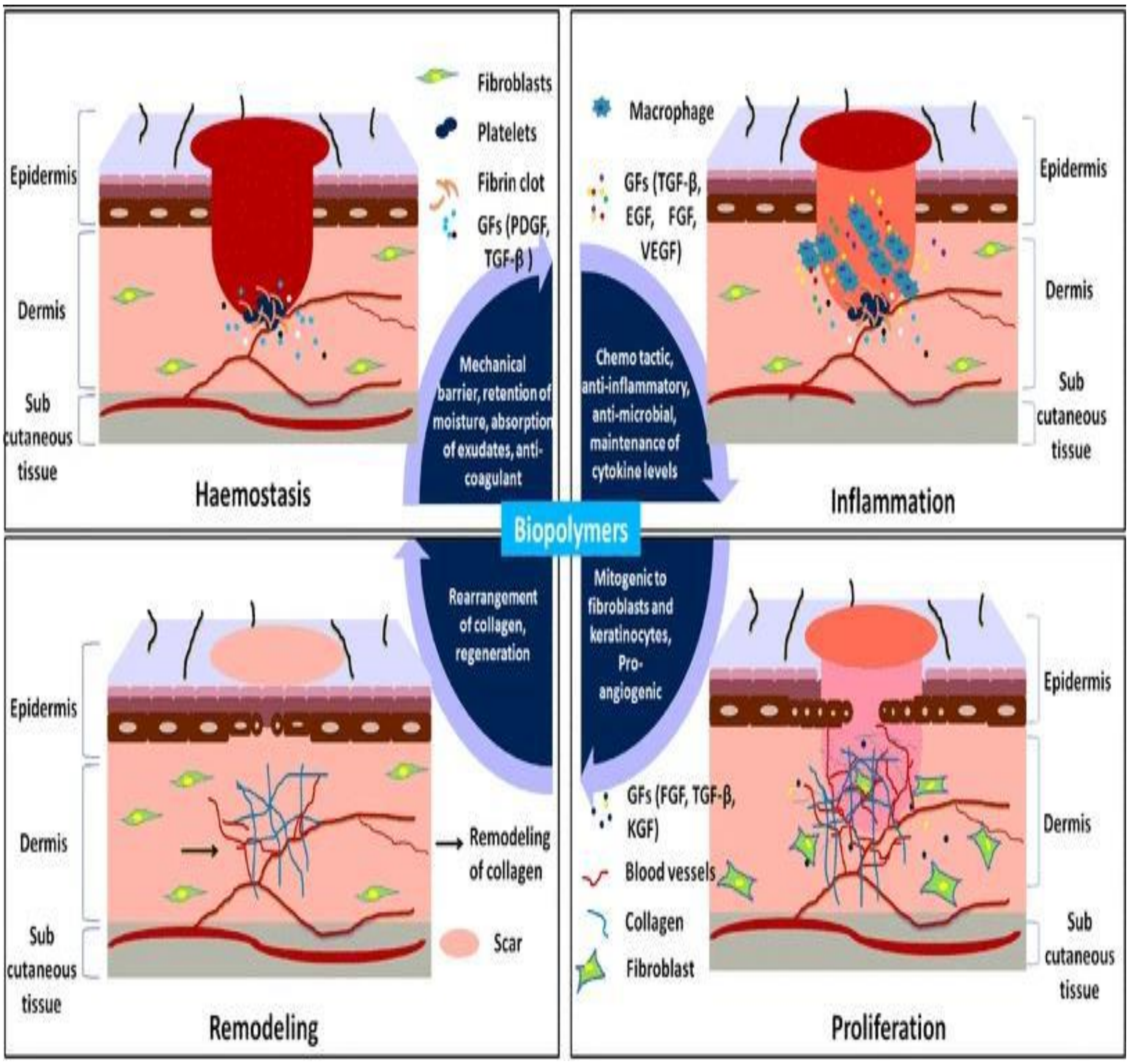
Polysaccharides have received considerable attention as functional biomaterials, due to their non-toxic, biocompatible, and biodegradable properties, for new and high-valued applications such as pharmaceutical, biomedical and cosmetic applications. Proper isolation and determination of the structural characteristics of the native bioactive polysaccharides from different resources allows for a clear understanding of biological action mechanism and the relation between structure and activity. In turn, this will help to modify or function non-bioactive polysaccharides to similar and more desirable bioactivities.

Conflict of interest

The authors declare no conflicts of intersect.

Figures and Table:

Figure 1: The biopolymers role during wound healing phases.



The four major overlapping phases; haemostasis, inflammation, proliferation and remodelling, of healing wounds in normal conditions.

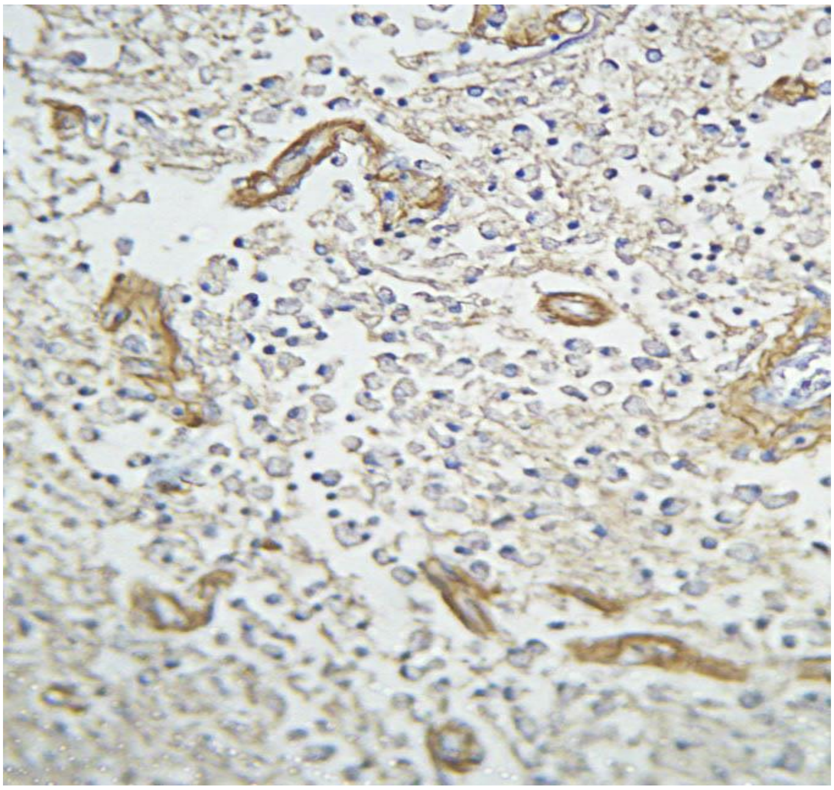


Figure 2: Immunohistochemical localization of Hyaluronic Acid (HA) in human affected tissue by using vector DAB solution. Microvessels stained positively for HA in stroke tissue, grey matter; (x400); (Source: AlQteishat A, *et al.,* 2006).

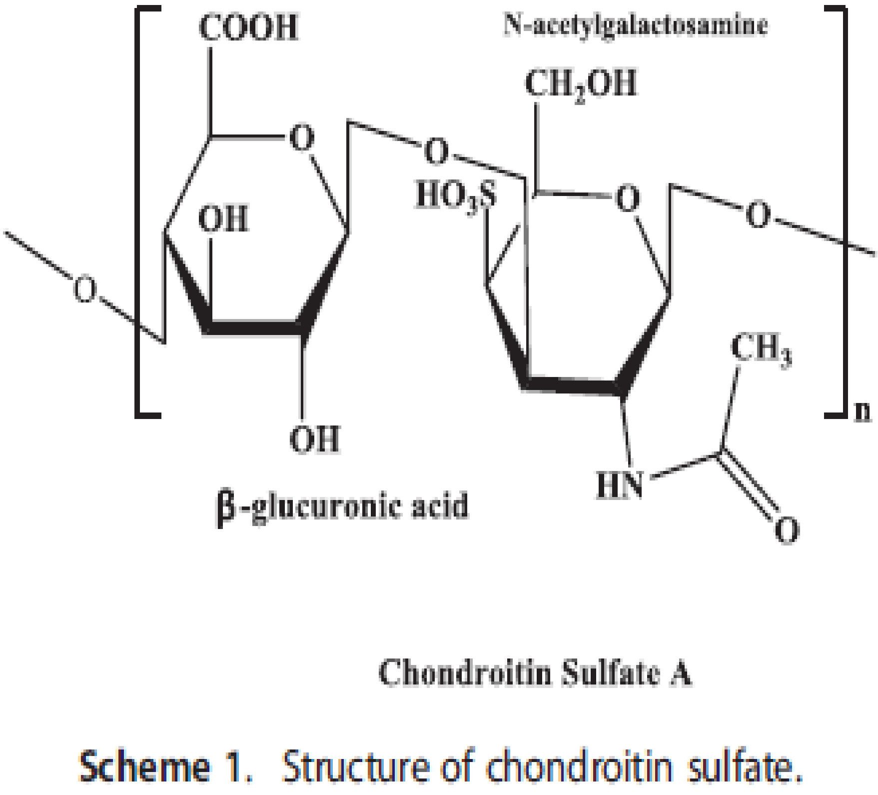
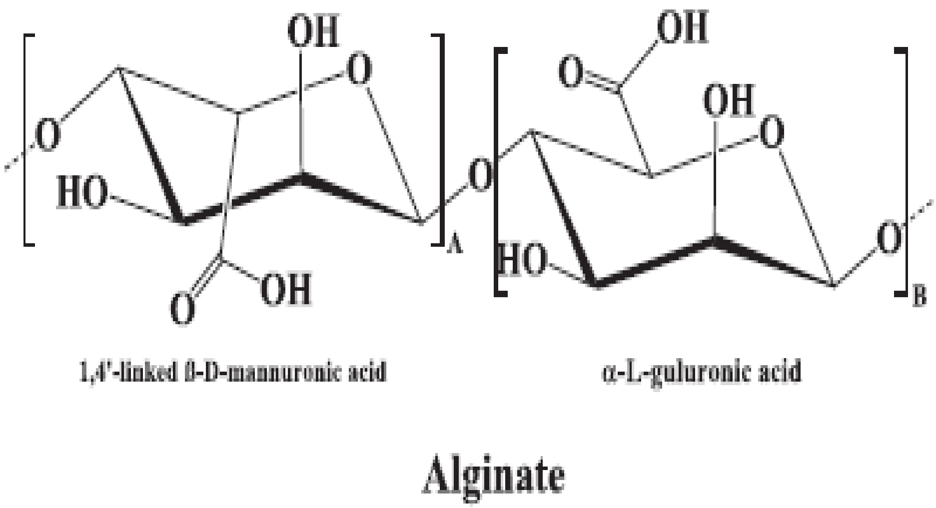
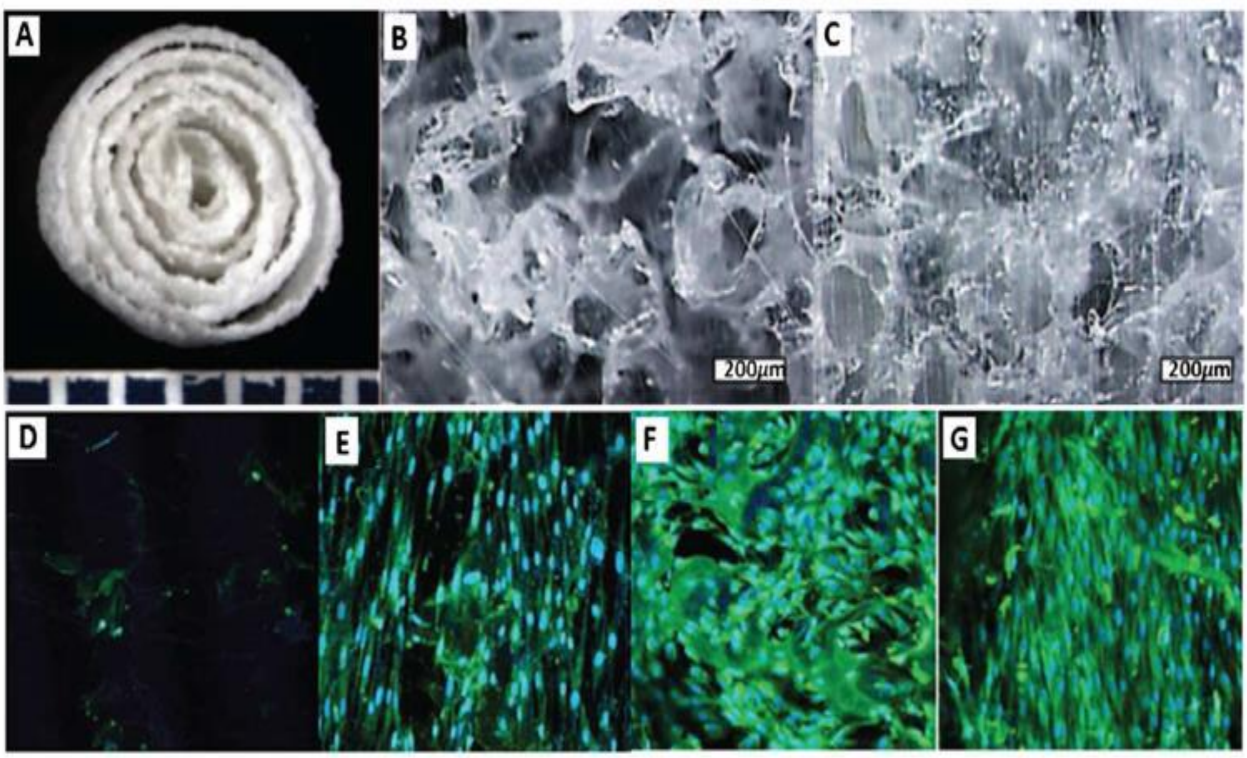


Figure 3: Structures of Chondroitin sulfate and Alginic acid.



Scheme 2. Structure of alginic acid.

Figure 4: Micro-Nano structured bioactive scaffolds for cartilage regeneration.



Optical micrographs of (A) macro-porous polycaprolactone (PCL) spiral scaffold, (B) macro-porous structures surface functionalized with sparsely spaced, random PCL-CS-HA nanofibers, and (C) macro-porous structures surface functionalized with sparsely spaced, vertically aligned PCL-CS-HA nanofibers. Representative laser confocal immunofluorescence images of aggrecan comparing (D) control PCL nanofiber scaffold with CS and HA without cells, (E) vertically aligned neat PCL nanofibers, (F) randomly oriented PCL nanofibers with CS and HA, and (G) vertically aligned PCL nanofibers with CS and HA following 28 days *in vitro* culture. Presence of CS and HA increased the levels of aggrecan expression. Protein expression and cell orientation was in the direction of fibre alignment. (Source: Lee, *et al.,* 2014)

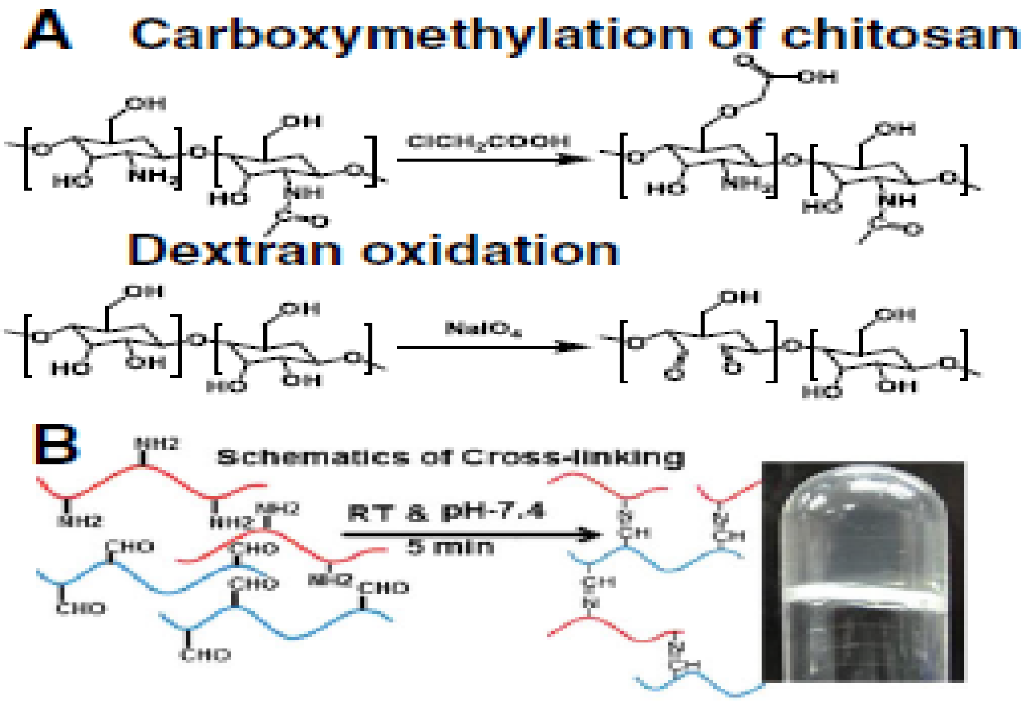


Figure 5: An example of *in situ* gelling chitosan-based hydrogel for bioactive factor and cell delivery.

A tentative reaction mechanism to create cross-linked chitosan-based hydrogels where (A) carboxymethylation of chitosan (CMC) and oxidative cleavage of dextran (DA) and (B) CMC-DA cross-linking resulting in an imine bond (Schiff base) formation. (Source: Cheng, *et al.,* 2014). RT = room temperature; min = minutes

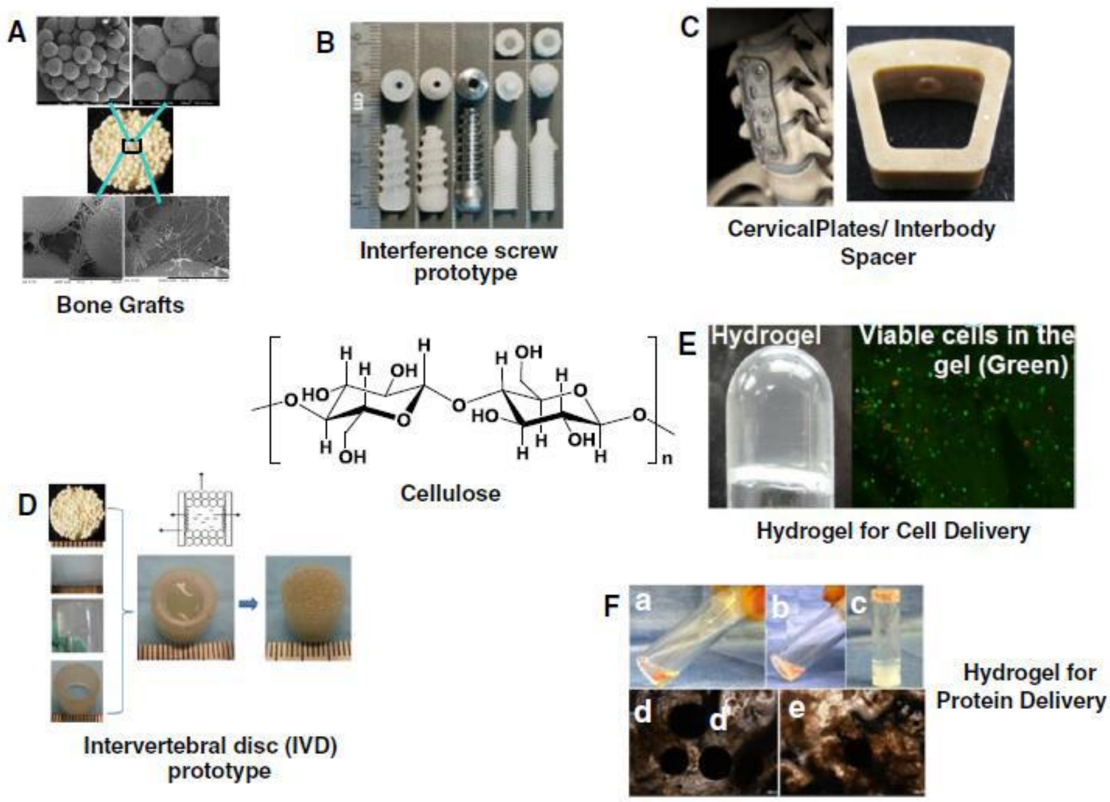


Figure 6: An example of cellulose material platform and its potential applications.

(A) Morphology of macro-porous and collagen functionalized micro-Nano structured scaffolds for bone tissue regeneration applications. (B) Examples of solid interference screw structures used for tendon and ligament graft fixation into bone, from left to right, are examples of commercial polyester, metal products, cellulose and its composite with hydroxyapatite. (C) Interbody spacer for spine fixation machined from the cellulose block created from compression molding. (D) An example of interbody prototype, which mimics three major intervertebral disc components including nucleus pulposus, annulus fibrosus, and a cartilage endplate. (E) and (F) are examples of injectable hydrogels as carriers for cell and therapeutic agents for a variety of tissue regeneration.

Table 1: The biopolymers characteristics and their role in healing process.

Biopolymer	Monomer units and linkage	Sources	Biological role
Collagen	Amino acids linked by amide linkage	Gelatin, etc.	Tissue regeneration, wound healing and bone remodeling
Cellulose	β-d-Glucose linked by β-1,4-glycosidic linkage	Plant cell wall and some bacteria	Moisture retention, accelerate and promote healing processes
Alginic acid	1-4 linked α-L-guluronic acid (G) and β-D-mannuronic acid (M) residues glycosidic linkages	Cell wall of brown macroalgae	Anti-inflammatory
Hyaluronic acid	*N*-acetyl-d-glucosamine and d-glucuronic acid linked by β-1,4 and β-1,3 glycosidic linkages	Animal origin	Endothelial proliferation and migration, anti-inflammatory and fibroblasts stimulation
Chitosan	β-(1→4)-linked D-glucosamine and *N*-acetyl-D-glucosamine glycosidic linkages	Crab- and shrimp shell, insects and fungi	Wound healing, drug delivery and tissue engineering
Fucoidan	α-l-Fucose linked by α-1, 3 glycosidic linkages	Brown seaweed	Proliferation of fibroblasts and the reconstruction of a skin and anti-inflammatory

Polysaccharides and their derivatives benefit from a non-toxic, biodegradable, bio compatible and lower expensive nature than its synthetic counterparts, compared with synthetic polymers. All of these merits do a broad spectrum of applications to endogenic polysaccharides and their derivatives in various fields such as biomedical and pharmaceutical, and cosmetic applications. Currently, polysaccharides play an important role in traditional health care and disease control, while many new fields of application, such as tissue and wound treatment, (both internally and externally) have also been explored. (Khan & Ahmad, 2013; Lindblad, *et al.,* 2007; Sandra, 2009).

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