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Biopolymer-based composites for tissue engineering applications: A basis for future opportunities

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ABSTRACT

Biomimetic scaffolds supporting tissue regeneration are complex materials with multifunctional characteristics. The unique biocompatibility and biodegradability of biopolymers make them excellent candidates for tissue engineering and regenerative medicine. Biopolymers, which have a wide range of properties, can be obtained from different natural sources. Depending on the target tissue, biopolymers can be engineered to meet a series of specific functions. We review different types of biopolymers and their composites, besides their interactions with specific cells and tissues. Specific cellular mechanisms in tissue regeneration are also considered to elucidate the effects of biopolymers on controlling cellular mechanisms given their advantages and challenging aspects. Furthermore, the modifications required to mimic the properties of neural, cardiac, bone, and skin tissues are discussed. Utilization of biopolymer-based composites in tissue engineering requires additional improvements, where several challenges should be overcome. This work is mainly focused on biopolymers used in tissue engineering, providing support for engineering of future biocomposites for the same purpose. Some examples of biocomposites are also provided, a general guide for selection of biopolymers and the secondary component (biopolymers as complements, additives, or nano-scale biomaterials) to develop biocomposites.

1. Introduction

Almost every ten minutes, one person is added to the national transplant waiting list in the United States as a consequence of disease- and injury-associated organ/tissue damages. Since organ donation still seems to be rare, about twenty Americans die every day due to the shortage of transplant organs. Tissue engineering and regenerative medicine provide biomedical engineers and doctors with appropriate

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strategies for replacing dysfunctional tissues/organs with biomaterials. Due to their unique properties, polymers play an essential role in tissue engineering applications. Polymers can be engineered in different ways and formed into various microstructures to achieve the desired performance. They are usually utilized as a supporting substrate in tissue engineering, which can carry the cell and the therapeutic agent to the targeted zone [1–6]. Among different forms of polymers used in tissue engineering are films, nanofibers, and hydrogels [7–16]. Since minimally invasive methods are prioritized in medicine due to the possibility of eliminating surgical processes, injectable hydrogels have been achieving significant clinical attention [17,18]. To attain maximum regeneration of dysfunctional tissues, a selected polymer should exhibit biocompatibility and controlled degradation rate. Accordingly, various biopolymers have been designed, and some of them commercialized as substrates for tissue regeneration [19–23].

Biopolymers have various uses and can generally be classified into agro-, microorganism-, and semi-synthetic polymers. The first generation of biopolymers were developed from agricultural feedstock including potato, corn, and other carbohydrate-containing resources. Natural polymers as a big clan of biopolymers' family are abundant in nature, mainly in the forms of polysaccharides or proteins. Biopolymers can also be categorized based on the processes through which they are obtained as of natural biopolymers obtained with some modifications (e.g. starch) [24–28], biomonomers obtained by fermentation, followed by polymerization (e.g. polylactic acid, PLA) [29–33], and biopolymers produced using bacteria, such as bacterial-cellulose and polyhydroxyalkanoates (PHA) [34,35]. Biopolymers exhibit excellent tissue biocompatibility and can be degraded within the body with minimum toxicity. These characteristics are attributed to natural sources from which they are taken. However, biopolymers cannot solely mimic specific tissue behavior, therefore, they have to be modified [36,37]. For instance, an injectable conductive chitosan was synthesized to deliver

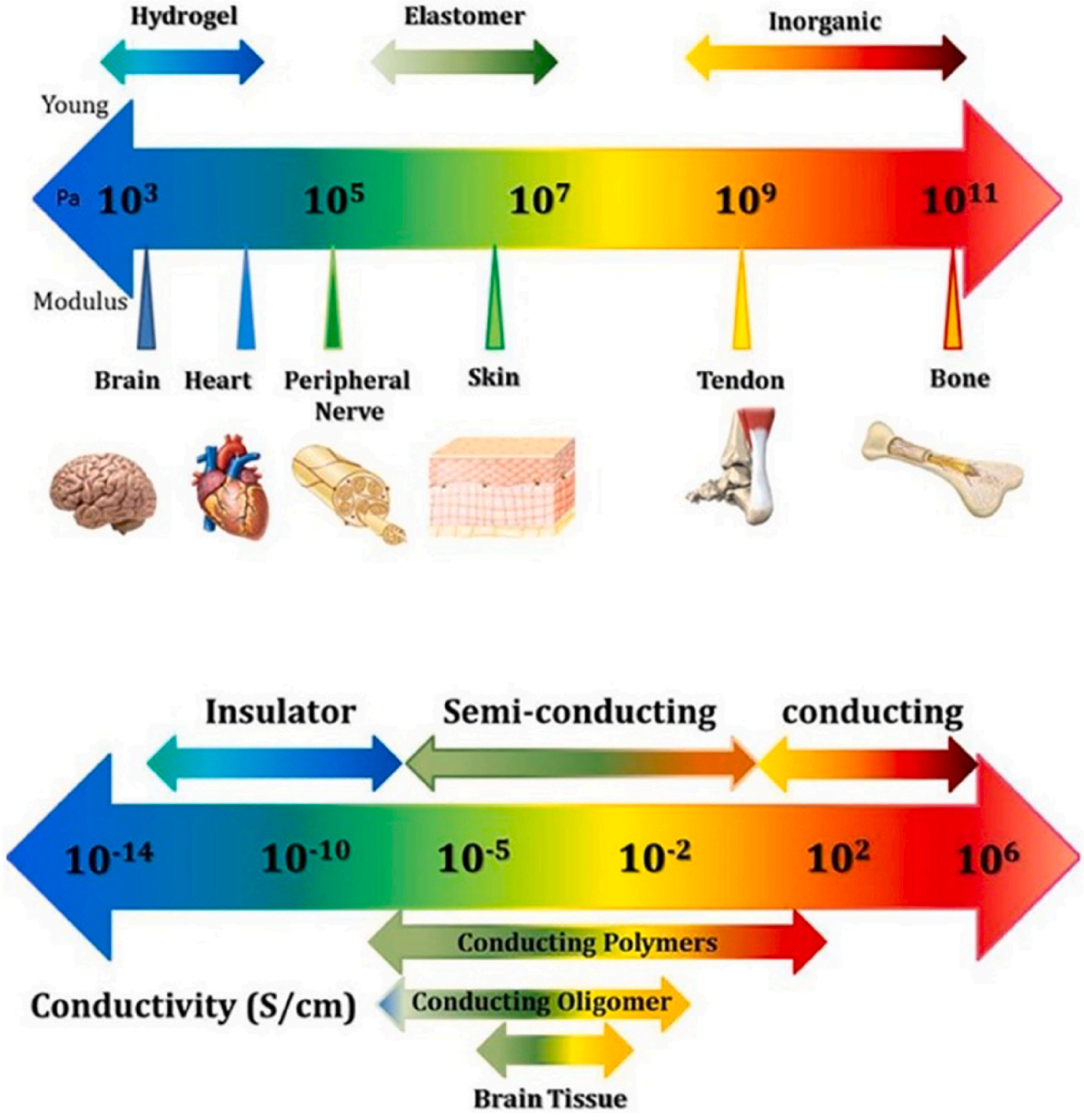

Fig. 1. Comparison of behavior of tissue as a function of the type of biomaterial. For example, brain is a soft tissue, whereas the bone is besy known as a hard tissue. Biomaterials selection for such opposed tissues should be considered in terms of mechanical strength of biomaterials. From conductivity point of view, brain has a conductivity similar to that of semiconducting materials. The chemistry of the utilized biomaterial should also be considered carefully, to make it able to resemble native extracellular matrix (ECM) needed for required level of tissue mimicking performance. Reprinted with permission from Ref. [38].

growth factors for hippocampus regeneration. Oligoaniline has been used to endow conductivity to chitosan so as to accelerate cellular activity and action potentials of neurons [38]. Nerve guidance channel conductive materials have been used to facilitate neural regeneration in view of higher activity of neural cells towards conductive substrates [39,40]. Fig. 1 shows the windows of tissue mechanical properties and conductivity. To mimic behavior of a tissue, polymers should be modified to afford adequate level of regeneration. Different functionalities can be endowed to biopolymers using synthetic polymers and different types of additives as well as nanoparticles to develop biocomposites [41,42]. For instance, hydroxyapatite has been added to biopolymer-based scaffolds to mimic bone structures and properties [43,44]. Magnetic nanoparticles have also been used in chitosan to achieve stimulus and controlled drug release [45]. Thus, targeted tissue features should be understood before designing a scaffold capable of mimicking the tissue behavior. Evidently, a conductive substrate is preferred for neural tissue engineering, while a conductive elastomer would be a better choice for cardiac tissue engineering [46].

In teh light of above examples, tissue engineering with biopolymers necessitates modification of biopolymers in the form of biocomposites. We hereby elucidate main strategies frequently considered for appropriate biopolymer selection for tissue engineering, and summarize recent advancements made in relation to the most frequently used biopolymers. Moreover, the main tissue-specific regeneration mechanisms underlying the performance of biopolymers in tissue engineering are generally discussed. Biopolymers developed for different tissue scaffolds such as neural, cardiac, skin, and bone are separately discussed to highlight the performance window and other details related to functional biopolymers. Biocomposites based on natural polymers are particulalrly stressed.

2. Biopolymers

Biopolymers are mainly categorized into three main groups: 1) Those obtained from agro-resources like starch; 2) Those obtained from microbial activities like polyhydroxyalkanoate, and 3) Those obtained *via* biotechnology assistance, like PLA (Fig. 2) [47].

Agro-based biopolymers can themselves be categorized into polysaccharides and proteins. Polysaccharides are the most abundant macromolecules in the biosphere. They are composed of glycosidic bonds, which are one of the key structural elements of plants and animal exoskeletons [48,49]. The most well-known polysaccharides are chitosan, alginate, pectin, starch, and agarose [50–53]. Proteins are a family member of agro-polymers that can be renewably produced by animals, plants, and bacteria. Most proteins contain linear polymers constructed from a sequence of up to 20 various amino acids. Protein-based biopolymers that are used as constitutes for tissue engineering scaffolds include soybean proteins, corn proteins, casein, and gelatin [54–56]. Table 1 summarizes the most important biopolymers used for tissue engineering.

3. Biopolymer-cell interactions

Cells are complex chemical systems in which various activities are orchestrated through a plethora of chemicals (e.g., proteins, RNAs, and small molecules) and molecular machines [68]. In addition, cells are continually interacting with their native microenvironment (e.g., nutrients, signaling molecules, ECM, and other cells) through a dense forest of biomolecules (e.g., glycoconjugates and glycoRNA) harboring on cells' surface [69]. The chemical identity and concentration of surrounding molecules, and also physicochemical and mechanical properties together with the microstructure of ECM/scaffolds affect the cells' behavior. Mechanistically saying, cells continuously collect various information (e.g., chemicals, temperature fluctuations, and mechanical clues) from their surrounding environment and respond to them accordingly. Indeed, any fluctuation in cells' microenvironment can result in altering the delicate equilibrium between the cells and their environment followed by cellular responses like proteins expression.

Various factors such as physicochemical and mechanical properties of the substrate can affect/change the functions and/or morphology of the cells [70]. Mechano-sensing mechanism in cells, which is usually mediated by the transmembrane proteins known as integrins, can detect mechanical cues in cells' microenvironment and transduce them intercellular, thereby creating biochemical signals. During the last few decades, extensive research studies have enhanced our understanding about cells-biomaterials interactions. These finding has enabled designing and fabricating more appropriate tissue engineering scaffolds and hydrogels with tailored mechanical properties, that can affect cellular behavior in a controlled and on-demand fashion [71]. The mechanisms underpinning the importance of physicochemical and mechanical properties of constructing biomaterials, particularly biopolymers are grounded on the degree of cellular interactions. Understanding the cellular interactions of biopolymers is the key for achieving the desired tissue regeneration. Therefore, this section provides the reader with a general overview on how biomaterials affect cell functions. We generally deal with some basic information, then specific

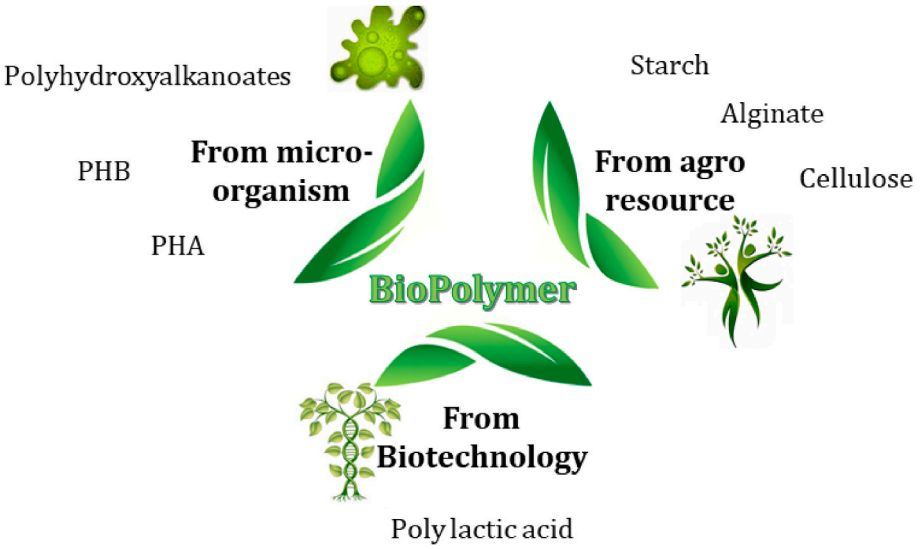

Fig. 2. A brief view of the most common classes of biopolymers in terms of their source or route of synthesis.

Table 1
Classification of the main biopolymers widely used in tissue engineering together with their main characteristics.

Biopolymers	Source	biopolymer	Properties	Ref.
	Agro-resources	Starch	Composed of α-d-glucopyranose homopolymer units, the amylose and the amylopectin and hydrophilic structures.	[57]
		Chitin	The second most abundant polysaccharide after cellulose, also known as the most abundant aminopolysaccharide polymer. Chitin is the building block of the crustacean's exoskeletons, insects, and the cell walls of fungi macrofibrils.	[58]
		Chitosan	Chitosan is the deacetylated form of chitin, which supports formation of polyoxysalts. It is known for its ability to form films, biocompatibility, biodegradability, non-toxicity, and molecular adsorption properties.	[59]
		Gelatin	Gelatin is achieved *via* collagen hydrolysis. The conversion degree of such a transformation is related to the pretreatment, process time, pH, and temperature.	[60]
		Alginate	Alginate is a linear polysaccharide, plentiful in the nature. Sodium alginate contains α-l-guluronic acid residues (G blocks) and β-d-mannuronic acid residues (M blocks), like changing guluronic and mannuronic acids.	[61]
		Agarose	Agarose is obtained from red algae, it is comprising agarobiose (disaccharide of d-galactose and 3,6-anhydro-l-galactopyranose) repeating units, and is a self-gelling polysaccharide.	[62]
		Cellulose	Most plentiful agro-polymer in the nature is cellulose, which has a crystalline structure. The main derivatives of cellulose are cellulose acetate and cellulose esters.	[63]
		Collagen	Collagen is the major ECM element of most connective tissues within the mammalian body, including one-third of all proteins available within the tissues.	[64]
		Hyaluronic acid	Hyaluronic acid is a linear polysaccharide without branches isolated from bovine vitreous humor. It is one of the vital elements of ECM.	[65]
	Micro-organisms	Polyhydroxyalkanoates	PHA is of polyesters family synthesized *via* bacterial fermentation. Polyhydroxybutyrate (PHB) is the simplest and yet the most famous member of PHA.	[66]
	From biotechnology	Polylactic acid	PLA is an aliphatic polyester with lactic acid units produced *via* bacterial fermentation from renewable sources. It is synthesized from lactic acid polycondensation or ring-opening polymerization of lactide monomer.	[67]

cellular interactions are discussed in terms of biopolymer-protein molecular interactions. For instance, Bueter et al. showed that in macrophage cells, the NLRP3 inflammasome (which has an essential role in Interleukin 1β **(IL**-1β) release) can be triggered by chitosan in a phagocytosis-dependent manner [72]. Yaun et al. observed that the megalin receptor on renal proximal tubule cells exerts significant effects on receptor-mediated endocytosis of chitosan [73].

Cell interactions with substrates and microenvironments such as cell adhesion exert important effects on tissue regeneration. Cell attachment processes include various biological actions, including cytoskeleton reorganization. Cell adhesion molecules (CAMs) that facilitate cell adhesion processes can be categorized into five main subcategories based on their structural and functional characteristics: cadherins, selectins (E, P, L), integrins, immunoglobulins, and other molecules [74,75]. These molecules interact with substrates and thereby affect the regeneration performance. For instance, the anti-inflammatory effects of fucoidan (natural polysaccharide) are associated with its interactions with scavenger receptors on the outer cell layer or selection [76,77]. Algal reduces the polymorphonucleated leukocytes (PMNs) attached to the autologous rabbit aortae. Anti-inflammatory and antithrombotic activities can be achieved using fucan sulfate, instead of heparin [78]. The astragalus polysaccharide has been shown to efficiently relieve cardiac ischemia-reperfusion injury (IRI). Human cardiac microvascular endothelial cells (HCMECs) were used to confirm the protective effects of astragalus under *in vitro* hypoxia-induced IRI conditions. Astragalus prevented the consistency between HCMECs and PMN in IRI by down-regulating the p38 MAPK signaling pathway and suppressing cohesive molecule expressions in HCMECs [79]. These examples suggest that cellular interaction can be engineered by the selection and combination of biopolymers altogether. As the most famous member of polysaccharides, chitosan has been vastly used in medicine. Fig. 3 shows different cell responses toward chitosan, which is best known as an attractive and favorable biopolymer for tissue engineering [80].

Scaffolds make direct contact with the inner sides of the body. When a substance gets into the body, an initial immune response is activated, and host ECM as well as plasma proteins join to contain, or wall off the injurious agent [81]. Such proteins accelerate cell attachments to facilitate tissue regeneration. Coating implants using bioactive substances increases protein adsorption, and fibrous capsule creation accelerates the wound healing process (Fig. 4 shows the wound healing mechanisms), decreases the rejection risk, and improves reendothelialization. After endothelium formation, the body is no longer unprotected against foreign substances and will halt immune response. Protein adhesion to foreign surfaces significantly impacts cell attachments to the scaffolds. This may adversely end in clotting factors adhesion, which induces thrombosis, causing stroke and other blockages. Some platforms interact with body microenvironments, such as biosensors or drug-delivery platforms, such that protein interactions with them inhibit their efficacy [82,83]. Protein-biopolymer interactions are mediated by hydrophobicity, intermolecular forces, surface energy, and ionic/electrostatic interactions. By elucidating their mechanisms of action, biomaterials can be controlled by machining, alloying, and other methods to yield their best performance for biomedical engineering [84–86].

4. Biopolymers targeted at tissue scaffolds

Tissue engineering substrates should be able to provide the tissue with a proper microenvironment facilitating cellular activity, growth, adhesion, differentiation, and proliferation; therefore, such substrates should mimic targeted tissue behavior. Depending on tissue, the type, chemistry, and cellular interactions of biopolymers vary, which should be considered in design and implementation of tissue repair and regeneration. Moreover, different sorts of diseases are arising from tissue and cellular responsiveness to biopolymers. Since selection of biomaterials is mainly based on target tissue, we deal with biopolymer selection for a given tissue engineering purpose.

4.1. Neural tissue engineering

The neural system is comprised of two parts: the central nervous system (CNS) and the peripheral nervous system (PNS). Due to the limited capacity for self-regeneration by neural organs, the neural system regeneration is a challenging issue in tissue engineering. Neural damage can occur as a consequence of accidents or neurodegenerative diseases such as Alzheimer's, multiple sclerosis, or Parkinson's [88–90]. In the CNS, reactive astrocytes and the formation of inhibitory glia scars inhibit damaged tissue repair. Nerve regeneration is supported by the Schwann cells (SCs) myelinating the axons in PNS, which assists axon digestion (phagocytosis) during the injury. After the injury, SCs support regeneration by targeting neurons to create a tunnel known as the

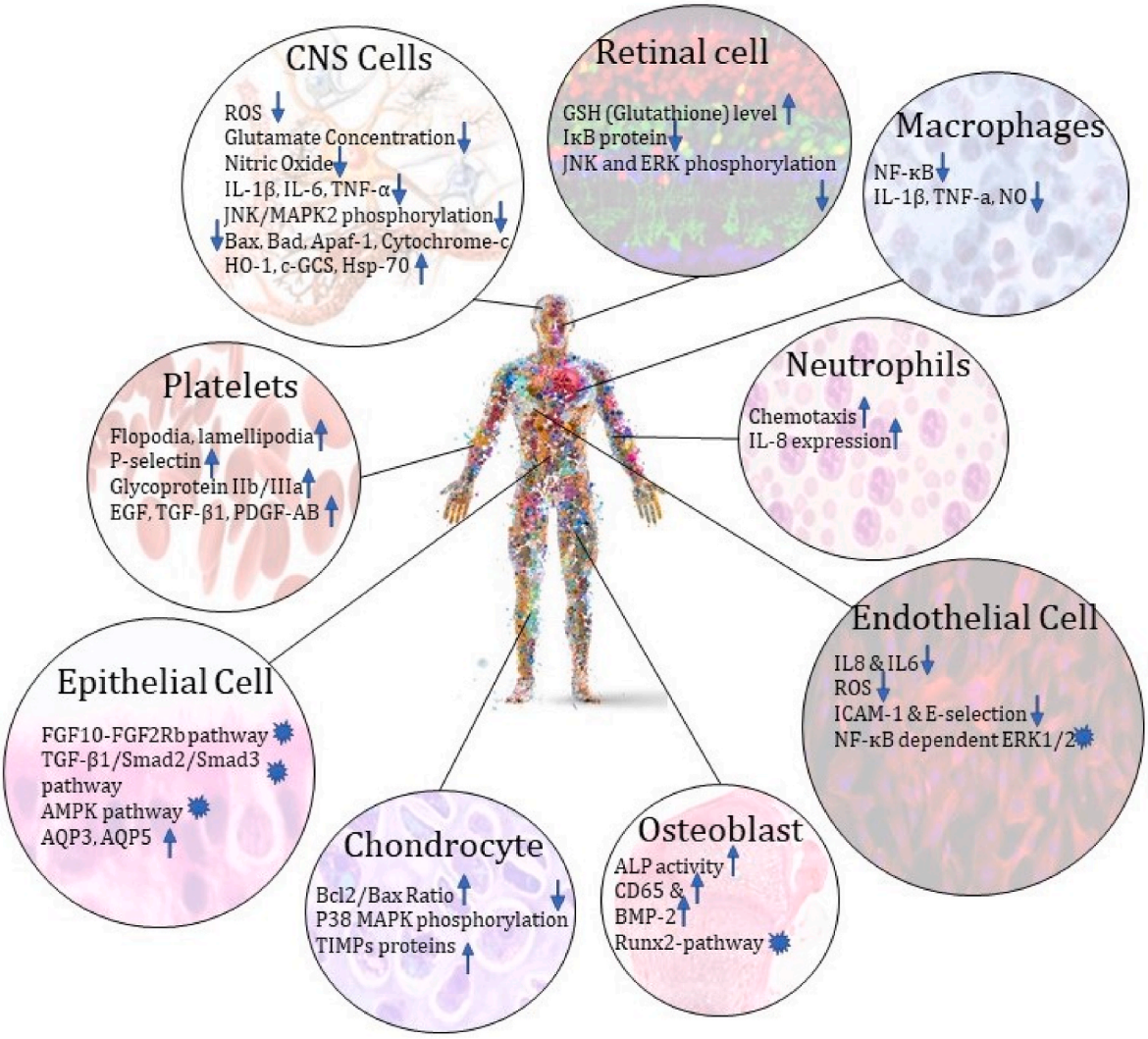

Fig. 3. Various cellular responses toward chitosan-family biopolymers (up arrow: enhance; down arrow: reduce; star: initiate).

''bands of Büngner'', a guidance path for repairing axons, acting as an endoneurial tube. Studies have aimed at developing suitable approaches to avoid extra damage and meanwhile stabilize the injured area. Nerve damage impacts the quality of life. Sensory and motor function deficits of the PNS result in paralysis of the affected limb and excruciating neuropathic pain through the mechanism shown in Fig. 5 [90,91]. Glia cells, neurons, inflammatory cells, and SCs are involved in PNS regeneration. Under proper conditions, the PNS can repair itself when small defects occur. After nerve injury, Wallerian degeneration is initiated *via* a sequence of cellular/molecular actions from distal sections of the damaged nerves to proximal sections. This phenomenon causes the axoplasmic disintegration of microtubules and microfilaments within one week [92]. During this period, the nucleus of damaged nerves is eccentrically located inside the cell bodies, while the nucleolus is protuberant. Additional proteins are synthesized to stimulate axonal repair, which alter neuronal performance. Variations in SCs proliferative genes, like growth-associated protein-43(GAP-43) enhance the rates of SCs proliferation to induce Wallerian degeneration. After damage, SCs alter their function from myelination to a more plastic and regenerative phenotype to break the myelin [93]. Thus, the introduction of lysophosphatidylcholine into the SCs is necessary for phospholipase expressions [94]. Moreover, SCs secrete cytokines that are essential for phagocytosis and macrophage recruitment to distal parts of damaged nerves [95]. Macrophages remove most of the myelin debris and remain *in situ* for more than 30 days [96]. Then, SCs growth is accelerated by mitogen factor inducement and alignment of endoneurial tubes to shape the structure of Band of Büngner for axonal guidance [97]. The bands of Büngner act as platforms for guiding axonal development in the time span of repair process. In the final repair stages, the sprouting cones lengthen (1–3 mm/day) *via* bands of Büngner to finalize axonal outgrowths and functional recovery [98]. Table 2 shows the most essential molecules involved in PNS regeneration.

For PNS damages smaller than 1 cm in size, end-to-end neurorrhaphy is the gold standard for treatment, whereas for damages having a size larger than 1 cm it is essential to use autologous nerve grafting for treatment. However, the lack of sufficient nerve grafts, neuroma growth, and immunological responses are challenging issues in autologous grafting. Therefore, the development of new strategies for neural treatment is of clinical significance. Polymers play an essential role in neural tissue engineering. Novel approaches have been proposed for CNS/PNS injury treatment including cell/therapeutic agent delivery, scaffold, hydrogel, and nerve conduits. Conductive substrates enhance cellular activity especially those of neural and cardiac cells [110]. Table 3 also covers neural conduits based on biopolymers. Atoufi et al. [111] synthesized a conductive alginate/agarose scaffold for tissue engineering. Agarose endows self-gelling properties to the system, thereby negating the use of toxic cross-linking agents [111]. In another study, agarose was coupled with conductive segments (oligoaniline). It was observed that PC12 cell attachment and proliferation were enhanced by the addition of the conductive segment [112]. Agarose should be used in

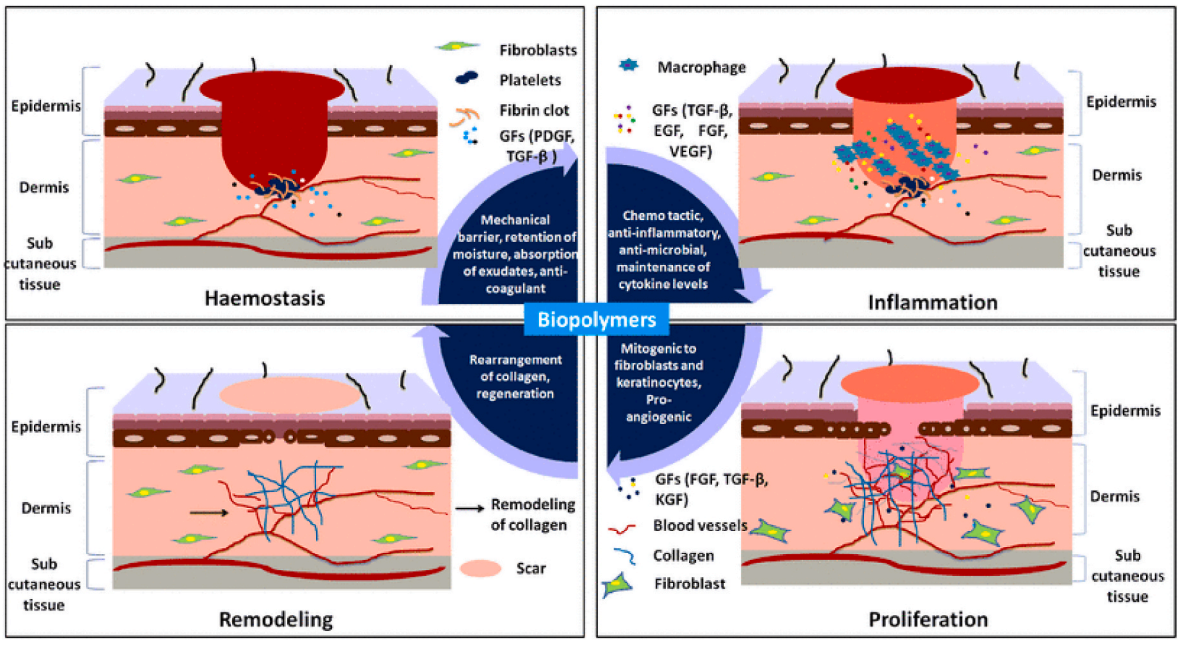

Fig. 4. Different phases of wound healing by using biopolymers. Reproduced with permission from Ref. [87].

the form of blend with other biopolymers or modified forms to support appropriate cell adhesion properties [113]. Wen et al. embedded nylon microfibers within the agarose matrix and found that subcellular filaments with diameters in the range of 5-30 μm can lead to the formation of aligned and neurite outgrowths in sympathetic neurons [114]. Alizadeh et al. used polysaccharide blends (agarose/alginate/chitosan) for neural disorder therapy. Aniline oligomer was used as the conductive segment to recapitulate neural behaviors and achieve electro-responsive drug release. The resulting hydrogel enhanced the differentiation of mesenchymal stem cells to dopaminergic neuron-like cells for dopamine supply in the CNS [115]. Agarose/gelatin/chitosan-aniline pentamers have also been used to differentiate human olfactory ecto-mesenchymal stem cells to promote motor neuron-like cells [116]. Schwann cell proliferation in damaged PNS enhances the axonal repair. It is also vital for damaged nerve repair. He et al. reported that chitosan promotes the proliferation and production of proliferating cell nuclear antigens (PCNA). Moreover, chitosan induced the mitogen-activated protein kinase/extracellular signal-regulated kinase (MEK/ERK) and phosphatidylinositil-3 kinase (PI3K)/Akt signaling pathways in SCs of rat models [117].

Nerve regeneration is a complicated process requiring several factors, signaling cues, and design factors to be effective (Table 4). PNS regeneration is aimed at inducing regenerative responses of proximal nerves to develop across the distal part and to improve functionality via synapsing with its original output [124].

4.2. Cardiac tissue engineering

A mature human heart has poor regeneration abilities. Cardiomyocytes (CMs) can be damaged by apoptosis, necrosis, and oncosis (ischemic cell death) leading to cardiac malfunctions. Necrosis (cell death due to injury) and apoptosis (automated cell death) are involved in pathological conditions of hearts. During cardiac pathogenesis, myocardial infarctions lead to the exchange of scar tissues and CMs sections with fibrillar collagen and fibroblast-like cells. Oncosis differs from necrosis in which the cell swells instead of being shrunk, yet in both cases, cells are damaged. While cardiac tissue engineering has not reached the clinical research stage, stem cell transplantation has exhibited satisfactory outcomes in clinical cardiac trials. Stem cell transplantation using polymeric-based scaffolds along external stimulation to repair damaged cardiac tissues has gained the attention of researchers [126]. Cardiovascular disorders are highly attributed to enhanced oxidative injuries to vascular endothelial cells. Reactive oxygen species (ROS) synthesis by vascular endothelial cells has a critical effect on the growth of several crucial clinical disorders, such as atherosclerosis and hypocholesteremia. Elevated ROS concentration in cells results in permanent damage *via* various mechanisms, such as the deactivation of vital enzymes, membrane lipids oxidation, and apoptosis initiation. Therefore, materials with the ability to lower free radical levels can protect cells from oxidative stress. Chitosan is a biopolymer with the ability to inhibit oxidative stress-associated damage [127]. In previous studies, 100–200 μg/ml chitosan significantly suppressed ROS concentrations to levels that were comparable to those of endogenous antioxidants (like SOD and GSH-Px), and inhibited lipid oxidation [128, 129]. Moreover, chitosan affects cytokine secretions by endothelial cells. The chitosan oligosaccharide (50–200 μg/ml) inhibited LPS-induced IL-8 production in endothelial cells by suppressing the p38/MAPK as well as PI3k/Akt signaling pathways [130], and down-regulated ICAM-1 (at 50–200 μg/ml) and E-selectin (at 200 μg/ml) expressions in endothelial cells by suppressing MAPK phosphorylation and NF-ƘB activation [80].

Mimicking tissue properties is essential in tissue engineering, therefore, cardiac tissue engineering scaffolds should be elastic and conductive [131–137]. Table 5 summarizes biopolymers used in cardiac tissue engineering. Sodian et al. synthesized polyhydroxyalkanoate with required elastomeric properties as a trileaflet heart valve. The synthesized scaffold exhibited biocompatibility, biodegradability, and elasticity properties, making it an excellent candidate for heart-valve scaffolds [138]. Ahadian et al. fabricated a conducive and elastomeric scaffold for cardiac tissue engineering. The used carbon nanotubes (CNT) as efficient nano-scale conductive materilas and intruded CNT into the biopolyester to develop a moldable elastomeric conductive scaffold [139]. Minimally invasive methods have been used in tissue engineering to reduce the side effects of surgical processes and costs. Injectable polymers have achieved this purpose. Huang et al. used collagen, matrigel, and fibrin glue (which are liquid at room temperature and solidify after injection at elevated temperatures) as injectable biopolymers. They found that the biopolymers enhanced angiogenesis and myofibroblast influx. Moreover, such biopolymers can be used for cell delivery and cell therapy [140]. Landa et al. synthesized injectable alginate for cardiac tissue

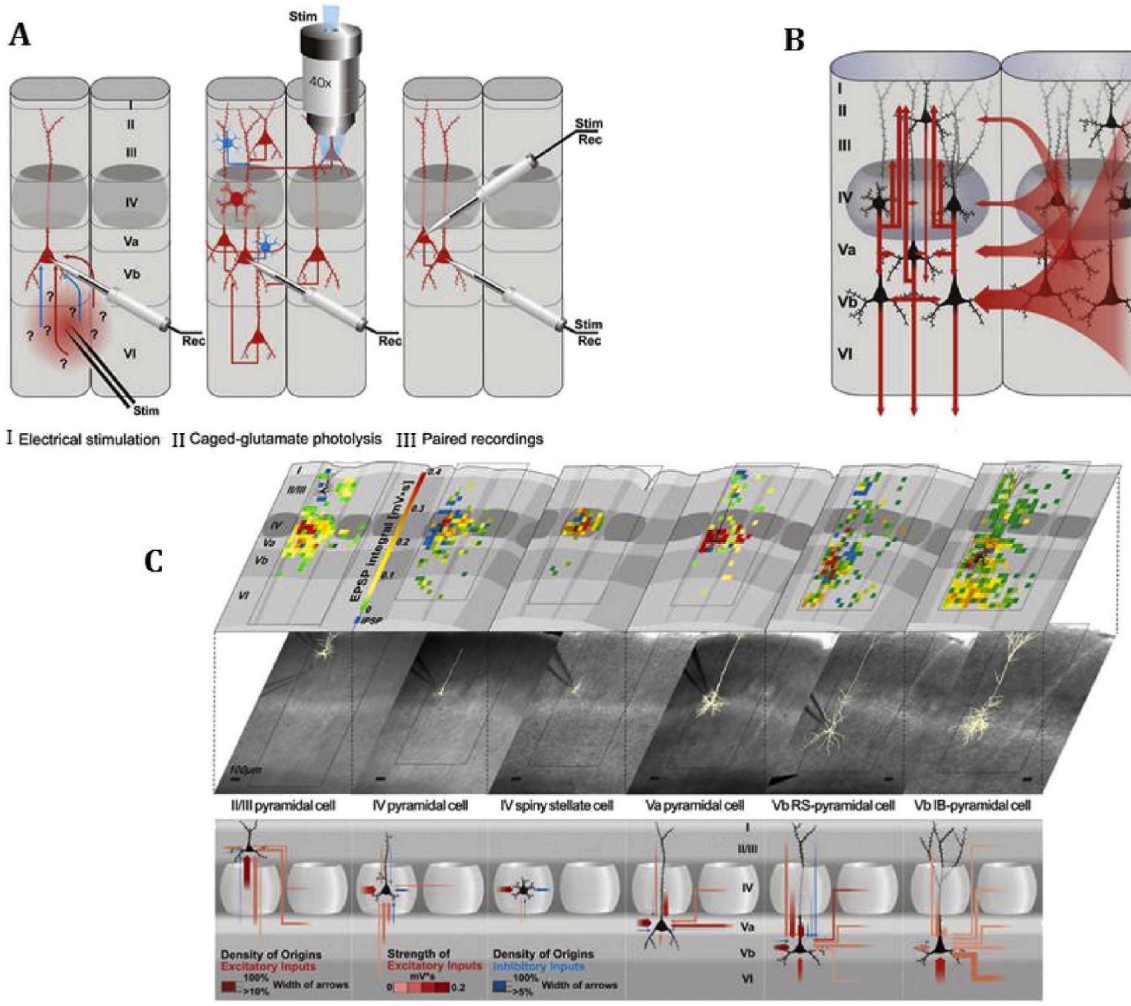

Fig. 5. The cortical synaptic connectivity evaluations; on (A) Different types of stimulations including electrical, photochemical, and paired recording. (B) The cortical columnar connectivity, which is the main feature for the integration and segregation of the sensory applications. (C) An overview of the final excitatory neurons for their potential monosynaptic intracortical applications. Reproduced with permission from Ref. [99].

engineering. The injected hydrogel had the ability to cover the damaged sections and within 6 weeks it was replaced by the connective tissues [141]. Variations in temperature, pH, and shear can cause polymeric phase transitions. Biopolymers can be used as injectable polymers either alone or by coupling them with other synthetic polymers, such as poly (N-isopropyl acrylamide). Collagen type I is normally dissolved in dilute acidic media, and at physiological conditions, it self-assembles to create a hydrogel. By neutralizing the acidic solution (pH = 7–7.4), collagen starts to cross-link within 30/60 min at 37 °C [142]. Chitosan is soluble in dilute acidic environments and forms hydrogels when the solution is neutralized. To achieve thermosensitive chitosan, β-glycerol phosphate endows thermosensitivity to chitosan [143]. Agarose, a self-gelling biopolymer, is widely used as a self-gelling hydrogel in tissue engineering [144]. For proper regeneration, such hydrogels are loaded with drugs, growth factors, or cells [145]. Dong et al. synthesized electroactive injectable biomaterials based on chitosan-aniline oligomer/dibenzaldehyde-terminated poly(ethylene glycol) (PEG-DA) and loaded the hydrogels with cells for cardiac cell therapy. Due to the dynamic covalent Schiff-base linkage between the amine group of chitosan and benzaldehyde groups of PEG-DA chains, such hydrogels exhibited injectability and self-healing properties [146]. Injectable hydrogel can also be prepared by oxidizing biopolymers, such as dextran or alginate, and also blending them with chitosan such that the oxidized group could react with the amine group to form a Schiff base. Based on this strategy, Zhao et al. synthesized the injectable hydrogel using oxidized dextran and chitosan [147].

4.3. Skin tissue engineering

The skin is the protective layer of the body against exogenous infections and diseases. It has two major layers, (*i*) the outer layer, the epidermis functions as an obstacle to the outer milieu, and (*ii*) the inner layer, also called dermis, which is comprised of the connective tissue [154,155]. Skin wounds can be categorized into different groups including superficial (just the epidermis), partial thickness (most of the dermis are healthy), full-thickness (the whole dermis, containing sweat glands and hair follicles are damaged), and complex (all layers are injured). Acute wounds such as chemical, burns, and surgical operation wounds repair within 2–3 months. However, chronic wounds including diabetic, infected wounds, and bedsores cannot heal within the normal duration. The delayed healing process and recurrence influence the sublayers, such as muscles and bones and causes tissue loss. Any factor that delays the switch from inflammation to proliferation, including systemic inflammatory disease, diabetes, and infections causes chronic wounds [156–158].

In skin wound repair, the skin healing process involves various cell activities, such as growth, migration, differentiation, and apoptosis. The typical wound healing process involves four overlapping stages: hemostasis, inflammation, proliferation, and remodeling (Fig. 6) [159,160]. Following damage, injured vessels are blocked by blood clots (which

Table 2
Molecules participate in PNS regeneration, their responsibility and target cells [100].

Molecules	Responsibility	Related cell	Ref
Lysophosphatidylcholine (LPC)	Myelin breakdown activation	Schwann cells	[94]
Interleukin 10 (IL-10)	Anti-inflammation	Macrophages	[101]
Growth-associated protein-43 (GAP-43)	Schwann cells proliferation and differentiation	Schwann cells	[102]
Nerve growth factor (NGF)			
Cell adhesion molecules (CAM)			
Neural cell adhesion molecules (NCAM)			
Glial fibrillary acidic protein (GFAP)			
Brain-derived neurotrophic factor (BDNF)			
Glial-derived neurotrophic factor (GDNF)			
Basic fibroblast growth factor (βFGF)			
Basic fibroblast growth factor (NT-3)			
Neuregulin's	Schwann cells proliferation and differentiation, axon remyelination	Injured nerve	[103]
Axon-derived calcitonin gene-related peptide (CGRP)	Formation of Bands of Büngner	Schwann cells	[104–106]
Neuregulin			
IL-1α/β			
Tubulin	Formation of Neuronal growth cones	Injured nerve	[107,108]
Actin			
GAP43			
Monocyte chemoattractant protein-1 (MCP-1)	Macrophage recruitment	Schwann cells	[109]
Monocyte chemo attractant protein-1α (MIP-1α)			

occur in the hemostasis stage), and phagocytes like neutrophils and macrophages migrate into wounded areas to remove the residues and to provide GFs to facilitate the proliferation stage. Different types of cells, such as keratinocytes, MSCs, endothelial progenitors, and fibroblasts migrate to the injury site, differentiate, and proliferate to heal the wounds, re-epithelialize, repair vascular systems, and develop granulation. Physical tension failure and contact inhibition in keratinocytes initiate signaling pathways facilitated by desmosomes and hemi-desmosomes, and then cytoskeleton reformation and keratinocytes migration/proliferation, particularly from the bottom layers of the wound margin. Moreover, re-epithelialization is facilitated by epithelial SCs of adjacent hair follicles and sweat glands. Keratinocytes secrete GFs and cytokines, including EGF, KGF, VEGF, and TGFβ to facilitate wound healing. At the initial proliferation stage, fibroblasts grow and secrete collagen type III to create new ECM at the wounded area [161,162]. In the remodeling stage, cells that are no longer necessary are removed from the wounded area and the ECM is remodeled to create the normal skin shape. In this stage, collagen III is replaced by collagen I by matrix-remodeling enzymes, such as matrix metalloproteinases. Collagen I has a higher tensile strength, relative to collagen III. A reduction in amounts of newly synthesized vessels is detected in the remodeling stage [163,164]. These processes occur at different stages of healing within the first-month post-injury (Fig. 6).

Effective wound healing necessitates the synchronization of various cells, cytokines, GFs, and ECM components. Interleukins (IL-1β, 6, 8, 10), tumor necrosis factor-α (TNF-α), transforming GFs, epidermal growth factor (EGF), VEGF, and the platelet-derived growth factor family altogether play important roles in healing process [166,167]. Neutrophils synthesize the pro-inflammatory cytokine (IL-1β), which enhances monocyte recruitment, increases the secretion of adhesion molecules in blood vessels, and promotes the endurance as well as retention of macrophages at injury sites. Macrophages secrete IL-10 (an anti-inflammatory cytokine) has a vital function in treatment. Basically, IL-10 regulates ECM synthesis, endothelial progenitor cell proliferation, inflammatory responses, and fibroblast cellular functions [168,169]. Important signaling pathways, including Wnt/β-catenin, Hedgehog, Notch, and several GFs/cytokine pathways are initiated in embryonic skin growth, and are triggered in postnatal cutaneous wound healing. ECM elements, like Extra-Domain-A (EDA) fibronectin, are produced in the postnatal wound healing process. Significant variations between molecular mechanisms that control postnatal cutaneous wound healing and embryonic skin development cause the repair of damaged skin to be unable to achieve its original state [170]. Wnt signaling has marked effects on different phases of cutaneous wound healing, e.g., hemostasis [171]. Wnt signaling is activated by injury and is involved in all healing stages, from controlling inflammation and apoptosis to the mobilization

Table 4
Strategies applied in designing Nerve Conduits [125].

Properties	Description
Biocompatibility	A scaffold should be compatible with surrounding tissues.
Degradability	The scaffold degradation should be accompanied by the nerve regeneration rate; the conduit structure should be designed to permit nutrient transition and reduce scar tissue infiltration.
Anisotropy	The inner structure of the scaffold causes an improved regeneration.
Modification with active molecules	Laminin and fibronectin coatings increase the cellular adhesion.
Physical fit	The conduit should fit with the nerve to prevent the nerve from squeezing.
Support cells	Schwann cells and stem cells enable to secrete neurotrophic factors, which enhances the regeneration.
Electrically conducting	A conductive substrate increases the regeneration and stimulates the nerve cells.

Table 3
Neural conduits based on biopolymers, their biological response, advantages and limitations.

Conduit	Loaded substances/cells	Biological assessment	Pros	Cons	Ref.
Chitosan	Alpha-lipoic acid	The sciatic nerve of Wistar rats with a 10 mm gap	alpha-lipoic acid improves the nerve repair process	limited mechanical strength, without conductivity	[118]
	Bone marrow	Goat peroneal nerve with 30 mm	strong potential in bridging the long gaps	limited depo period, limited mechanical strength	[119]
Gelatin	Tricalcium Phosphate	The sciatic nerve of Wistar rats with a 10 mm gap	ECM-mimetic structure	crosslinking agent displays cytotoxicity, limited mechanical properties	[120]
Collagen	Cerebrospinal Fluid	Male rats with a 10 mm gap	ECM-mimetic structure, improved regeneration, and functional recovery	Expensive	[121]
Cellulose	SCs and pyrroloquinoline quinone	Sprague–Dawley male rats with a 10 mm gap	increased restoration of motor function	limited mechanical strength	[122]
PLA	SCs	Lewis rats with a 10 mm gap	SCs secrete bioactive biomolecules and offer an improvement in the migration of axons.	fragile	[123]

Table 5
Biopolymers applied in cardiac tissue engineering together with their advantages and disadvantages.

Biopolymer	Advantage	Disadvantage	Ref.
Chitosan	Biodegradability, non-immunogenicity, mucoadhesiveness, antimicrobial properties, cytocompatibility, hemostatic feature	Limited solubility at physiological pH, limited mechanical properties	[148]
Alginate	Proper biocompatibility, biodegradation, non-thrombogenic feature, affordable cost, moderate and ionic gelling mechanism, non-antigenicity, and chelating capability	Minimal protein interaction, limited mechanical properties	[149]
Gelatin	High biocompatibility and biodegradation	Low melting point, easily dissolving in water, Limited mechanical strength	[150]
Collagen	Excellent biocompatibility, biodegradability, hyposensitivity, low immunogenicity	Limited mechanical strength and non-conductive	[151]
Fibrin	Biocompatible degradation residue, high elasticity, high biocompatibility, adjustable degradation rate, enhance cell attachment	Tend to shrink, low mechanical Performance susceptible to transmitting disease, Poor mechanical and electrical properties The low melting temperature, rapid dissolving In-water low protein adsorption	[152]
PLA	Proper Biocompatibility, suitable biodegradability, nontoxicity	Low mechanical performance, brittle	[153]

of stem cell reservoirs within wounded areas [172]. As a transcriptional co-activator, β-Catenin signaling and T cell factors/lymphoid enhancer factors regulate gene expressions to affect the healing process [173]. Various cytokines and growth factors, including epidermal GFs (EGFs), TGF-βs, vascular endothelial GFs (VEGFs), PDGFs, fibroblast GFs (FGFs), and various pro-inflammatory cytokines such as interleukins, play vital roles in the wound healing process [174]. Macrophages and fibroblasts secret TGF-βs, which bind serine/threonine kinase TGF-β receptor I and TGF-β-receptor II heterodimers to trigger the Smads. These molecules play different roles in healing processes. TGF-β1 and TGF-β2 affect postnatal healing and skin formation (hair follicle development) [175]. The Notch signaling pathway is involved in epidermal differentiation, vascular angiogenesis, and in crosstalks with Wnt/β-catenin and Hedgehog pathways [176,177]. Finally, the Hedgehog signaling pathway has significant effects on different phases of embryonic development, including skin morphogenesis and angiogenesis, and skin and hair follicles development (Fig. 7) [178].

Elucidation of the effects of the skin tissue engineering scaffolds on healing processes is important to achieve skin regeneration and wound healing [179]. Chitosan enhances PMN cell migration and wound healing. Two probable mechanisms are proposed: (1) Stimulation of IL-8 excretion from neutrophils and, (2) Complement activation. Chitosan leads to overexpression of IL-8 (chemotactic agent for neutrophils) by neutrophils, and such expressions are directly correlated with acetylation degree. Moreover, the acetylation degree affects hydrophobicity and chitosan interactions with PMNs [80,180]. During tissue regeneration, chitosan enhances macrophage functions in inflammatory responses, antigen presentation, phagocytosis, synthesis of various cytokines as well as active ingredients (TNF-α, IL-1β and nitric oxide (NO)) and the secretion of growth factors [181,182]. Calcium alginate exerted satisfactory effects on skin ulcer healing and collagen synthesis [183]. Drug addition to the biopolymers exhibited synergistic effects on wound healing. Simvastatin was loaded in the alginate dressing for wound healing, promoted Akt and Erk signaling to participate in angiogenesis, and upregulated HIF-1a and HIF-1a-mediated VEGF expressions [184]. As a natural fibrous protein, silk fibroin (SF) from Bombyx mori is an attractive biopolymer that has been used in wound healing. SF improves cellular activities such as proliferation, differentiation, as well as adhesion [185] and accelerates the healing process via NF-kB signaling, which mediates IKKα, IKKβ, and p65 expression, as well as IκBα degradation [186]. In normal skin, fibroblasts facilitate connective tissue repair and tissue remodeling [187,188]. Peptides from trypsin SF digestion enhance fibroblast proliferation [185]. SF supports fibroblast adhesion and proliferation [189]. Moreover, collagen addition to silk enhances fibroblast proliferation, which is important for healing (Fig. 8) [190].

Due to proper biocompatibility, affordable cost, hemostatic performance (SF interaction with fibrinogen and blood platelets), improvement of cell migration and cell recruitment, exudate absorbing performance, proper mechanical properties and elasticity, enhancement of cell attachment, migration, proliferation and differentiation, SF has been widely used for wound healing [193]. Other biopolymers, such as keratin, have been shown to accelerate the healing process. Wang et al. used keratin as a wound dressing, which facilitated the healing process [194]. Alginate has also been widely used in wound dressing applications. Commercial alginate for wound dressing is available. Wang et al. reported that alginate facilitates the healing process of diabetic wounds by up-regulating the ratio of collagen types I/III [183]. Biopolymers have the potential for wound dressing [195,196]. Table 6 shows biopolymer usage in wound healing.

4.4. Bone tissue engineering

Autologous bone as a highly efficient technique for bone regeneration is known as the “gold standard” clinical method. This method enhances bone development by osteoconduction (direct bone bonding) and osteoinduction (SCs differentiation into bone cells) and does not activate any immune responses [207]. About two million bones are grafted each year and are associated with various challenges, such as supply shortage, donor morbidity, and a 50% failure rate [208]. Hence, there is a need to establish suitable bone scaffolds based on biomaterials to enhance bone repair [209,210]. Polymers exhibited good biocompatibility, degradability, adjustable structural feature, and acceptable mechanical properties. To prevent the challenges associated with full bone regeneration, biodegradable polymers are vital for these kinds of repairs. The most common polymers in bone tissue engineering are collagen, chitosan, alginate, and silk as natural polymer as well as poly (lactic-*co*-glycolic acid) (PLGA), polycaprolactone (PCL), PLA, polydioxanone (PDS), and polyglycolic acid (PGA) as synthetic polymers [211–214].

Bone remodeling is a dynamic process that preserves the bone structure, regulated by osteoblast development and osteoclast-mediated bone resorption (Fig. 9). Perturbation in bone remodeling inhibits bone healing and causes bone disorders, such as osteoporosis and bone defects. Bone fractures and osteoporosis cause major disabilities. Following fractures, healing occurs spontaneously to regain the natural physical/mechanical characteristics of bones. Fracture healing involves the initial inflammatory phase, the repair phase, and the late remodeling phase. Osteogenesis, an outcome of osteoprogenitor proliferation, and matrix/osteoblast maturation have important roles in fracture healing. Drug therapy cannot fulfill the regeneration process. Therefore, designing suitable biomaterials to improve osteogenesis is essential for bone fracture and defect repair [215–217].

Various molecular and cellular actions are involved in bone development and fracture healing [219]. The involved mechanisms are associated with expressions of genes for osteoblast differentiation. As an essential transcription factor, Runt-related transcription factor 2

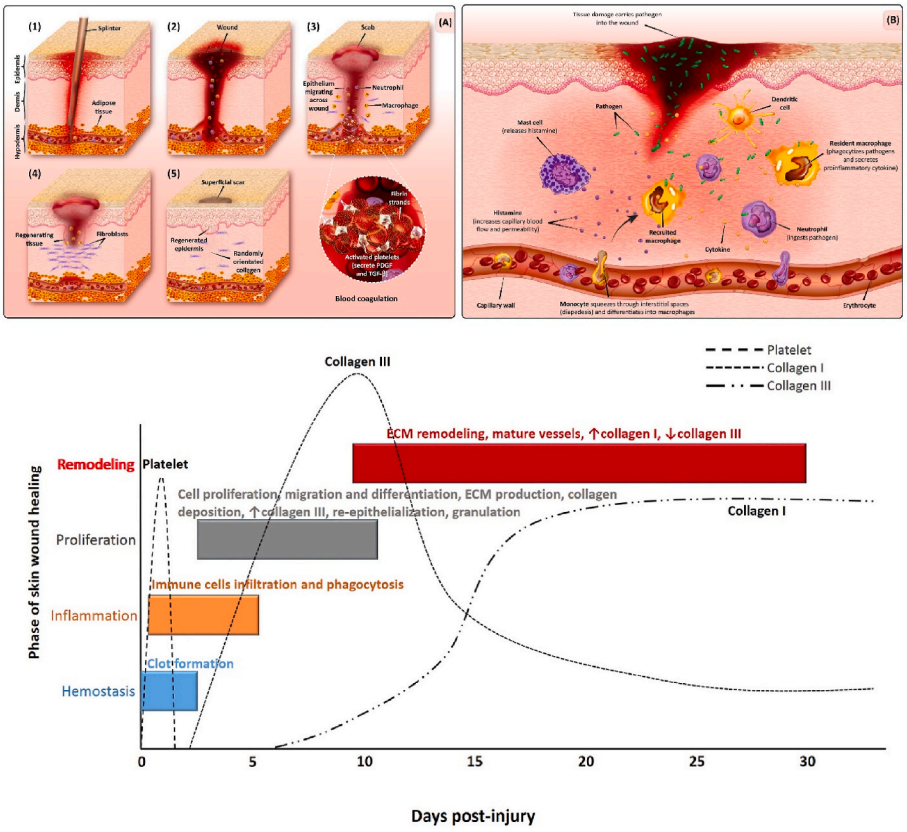

Fig. 6. Formation of the wound and healing process. (A) Healing stages: hemostasis, inflammation, proliferation, and remodeling; (B) Large wounded-area can be contaminated by bacteria that require proper antibiotic treatment. Inflammatory cells transfer to the damaged area by enhancing the penetrability of the capillaries. By enhancing the bloodstream, vital factors and cells go across the intravascular area within the extravascular area. Macrophages and neutrophils have an essential role in cleaning pathogens at the injured site. Reprinted with permission from Ref. [165]. Graph in the bottom demonstrates normal healing procedure stages in the first month after wound appeared. Reprinted with permission from Ref. [156].

(Runx2) has a role in osteoblast differentiation and mineralization [220]. During osteogenesis and bone remodeling, osteocalcin (OCN) and alkaline phosphatase (ALP), as two standard osteoblast biomarkers, are involved in controlling osteoblast action and mineralization of the ECM. Upregulating of such biomarkers in osteoblasts is associated with cell differentiation and maturation [221]. In bone regeneration, natural polymers because of their biocompatibility and biodegradability have attracted more attention, compared to synthetic polymers. Such polymers offer well-designed structures by acting as ligands to attach to cell surface receptors and provide enzymatic degradation spots [222]. For instance, as a biodegradable, biocompatible, and low immunogenic natural polymer, silk fibroin (SF) is suitable for tissue regeneration. Moreover, SF has a remarkable ability to induce bone repair due to structural similarity of the fibrous structure of SF to collagen I. Chitosan is another biopolymer that facilitates bone remodeling. It is preferred for bone regeneration because of its good biocompatibility, degradability, and antibacterial properties. Since chitosan does not have inherent osteoconductive properties, chitosan-based composite scaffolds have been synthesized to mimic bone performance. Chitosan biocomposites, along with hydroxyapatite or calcium phosphate, exerted proper effects on bone healing [223]. Nanofibers of chitosan-activated Runx2 mRNA and protein were fabricated, and the ALP, alizarin red, and von Kossa-staining examinations revealed that such fibers increased mineralization of osteoblast and stimulated proliferation of osteoblast and maturation via Runx2-mediated regulation of osteoblast-associated osteopontin, osteocalcin, and ALP gene expression [224,225].

The combination of particles with biopolymers enhances their mechanical behaviors and adjusts the structural characteristics of the platform to emulate bone structures [226–229]. Biomineralization is an effective procedure for developing nano-featured structures. In this process, porous scaffolds can be soaked in SBF, which provides Ca^{2+} and PO_4^{3-} which the in vitro apatite formation on scaffolds in SBF can be utilized for calculating the in vivo bone formation. The mineralization process on biopolymers facilitates because of the charged pendant groups on biopolymers which tend to nucleate apatite. Functionalizing using negatively charged groups such as carboxylate and phosphate groups as well as nucleation agents such as calcium phosphates (CaPs) and anionic proteins has been widely used for electrostatic inducement of mineralization. In this regard, various biopolymer/CaPs scaffolds have been used for bone regeneration [230]. Hydroxyapatite (HAp) as the steadiest CaPs in biological fluids that mimic bone properties, has been widely used in the polymeric matrix as a proper bioceramic. It is osteoconductive, biocompatible, low immunogenic, and has the ability to directly bind to hard tissues. Such ceramics are normally developed using phosphates from fluids in the vertebrate's body at a pH range of between 7.2 and 7.4. Due to its high bon affinity, HAp is a suitable candidate for bone allograft and metal-based implants [230–232]. Table 7 summarized the properties of biopolymer/CaP composites. For instance, culturing cells on the framework and/or scaffolds of chitosan-based nanomaterials with different compositions of polymers and natural components revealed different cellular densities and also morphologies (Fig. 10) [233].

4.5. Cartilage tissue engineering

Osteochondral defects (OCD) and anterior cruciate ligament (ACL) are prevalent articular cartilage diseases (ACD). It is anticipated that in the near future, OCD will affect 35% of the population to become the main cause of disability. Incidences of OCD are associated with age, sex, and loaded stress. While surgical OCD treatment is helpful, post-surgical regeneration of the cartilage remains a challenge that is correlated with low metabolic functioning of the cartilage. Moreover, the long healing time of internal articular cartilage necessitates innovative approaches for restoring the cartilage, not including surgery [250]. As a soft flexible tissue covering the bone ends at the joints, the cartilage preserves the bone from mechanical loading. Cartilages are categorized into three

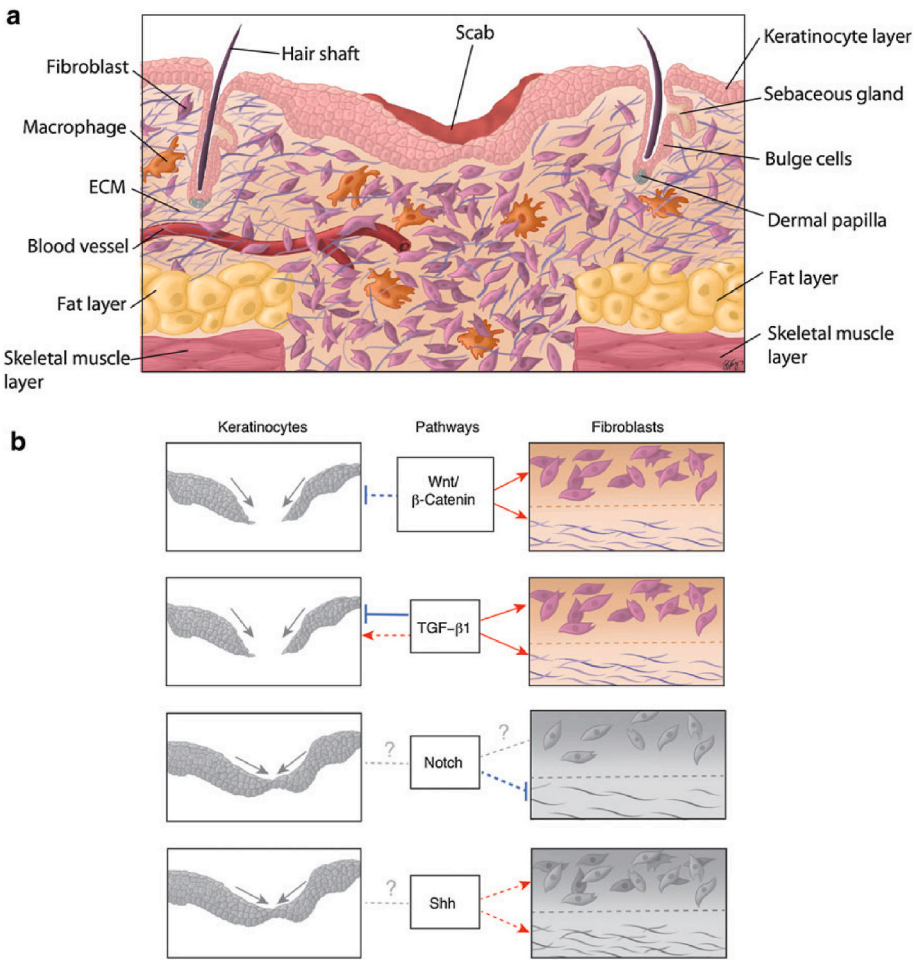

Fig. 7. Schamatic regeneration of cutaneous wound healing. (a) Cutaneous wound in the period of the proliferative stage of healing. Repairing dermis is augmented with a superior amount of fibroblasts and macrophages in comparison to normal skin. (b) The impact of the signaling path on keratinocyte performance in epidermal closing, fibroblast actions, and matrix deposition in dermal reorganization. Red signs show a progressive impact on a cell type/outcome. Blue signs show a negative impact. Solid lines declare the proven in vivo impact. Dotted lines are based on in vitro studies. Gray dotted lines with a question sign show undetermined outcomes. Colored and gray diagrams are based on *in vivo* and *in vitro* studies, respectively. Reprinted with permission from Ref. [170]. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

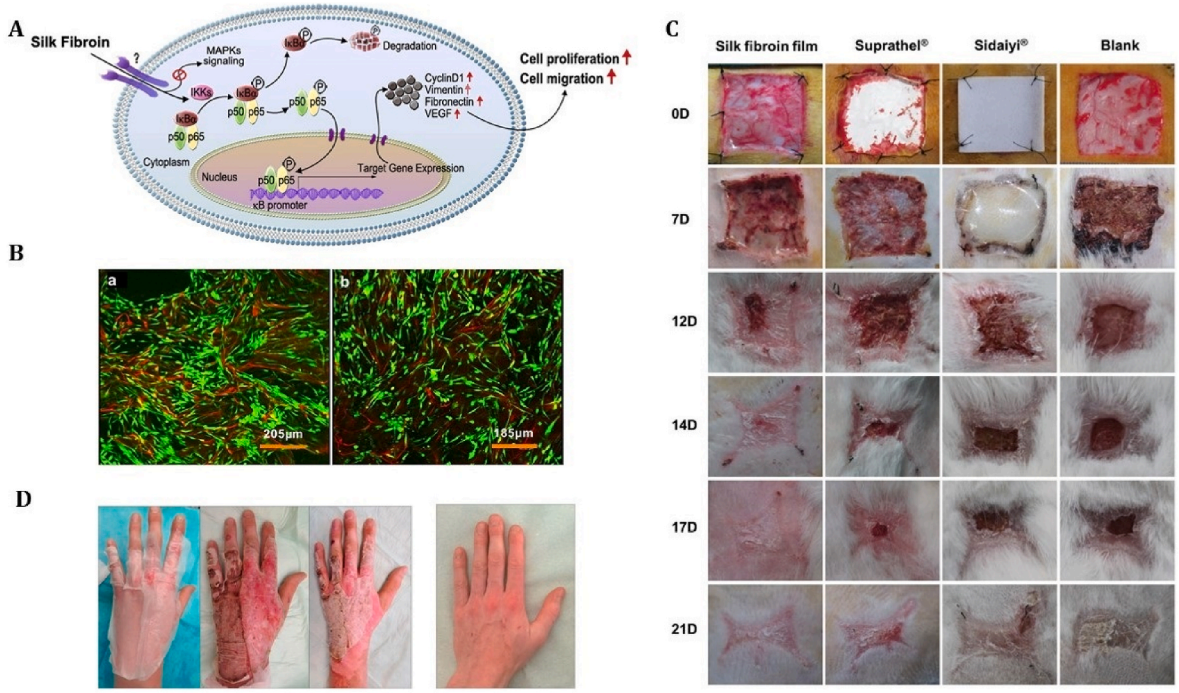

Fig. 8. (A) SF in the healing process using NF-κB signaling pathway. Reprinted with permission from Ref. [186]. (B) fibroblasts Viability on silk/collagen scaffolds after day 11. (a) silk with 7.4% collagen, and (b) silk with 20% collagen. Reprinted with permission from Ref. [190]. (C) Morphology of the wound healing process within 21 d using SF. Reprinted with permission from Ref. [191]. (D) Patient with a hand burn treated with silk-based wound dressing after 1 month [192].

Table 6
Biopolymers used in skin tissue engineering, together with their mechanism of action, properties and dressing suited to them.

Biopolymers	Healing Mechanism	Properties	Wound dressing Type	Ref.
Chitosan	Through the initial healing cascade, chitosan exhibits hemostatic performance and promotes neutrophil infiltration/ migration, macrophage, and increase fibroblast migration also conducts collagen deposition, as experienced in the case of diabetic mice.	Proper biocompatibility, biodegradability, antibacterial performance, and mucoadhesive feature.	Hydrogel, hydrocolloid, film, porous scaffolds, Nanofibrous mats	[197]
Alginate	Alginate maintains the moisture of the wound, reduces the bacterial activity, and facilitates the healing process. Calcium alginates improve cellular activities.	Proper biocompatibility, and adjustable biodegradability. improve cell growth and survival.	Hydrocolloid, nanofiber, hydrofiber, hydrogel	[198]
Silk	Silk facilitates collagen synthesis and deposition in the wounded area, it also increases epithelialization.	Promote the proliferation of fibroblasts, and keratinocytes	Films, scaffolds, ointments	[165]
Gelatin	Gelatin promotes signal transmission and adhesion of cell.	Biocompatible, non-immunogenic, biodegradable.	Hydrogels, microgels, sponges	[199]
Fibrin and fibrinogen	Fibrin and fibrinogen facilitate the hemostasis stage of wound cascade, promote the migration, attraction, proliferation, and adhesion of a cells.	Biodegradable, biocompatibility with low toxicity.	Scaffolds, nanoparticles, bandages	[200]
Cellulose	Cellulose promotes wound healing at an early stage and regulates trans epidermal water loss. It also decreases moisture loss without extreme.	High swelling ratio, enhanced biocompatibility with mucous membranes, non-toxic, and cost-effective.	Hydro fibers, films Hydrogel, sponges	[201]
Collagen	promotes ECM deposition and cell adhesion, nutrients transportation, acts as a regulatory factor and enhances gaseous exchange to allow the survival of cells.	Biocompatible, and crosslinkable at elevated temperatures.	3D scaffolds, Hydrogel Films, sponges	[202]
Chondroitin sulfate	Chondroitin sulfate promotes wound healing, increases fibroblasts expression, activates wound healing cascade, stimulates wound repair.	Biodegradable, biocompatible, with low toxicity.	Nanofibers, Scaffolds, transdermal patches	[203]
Hyaluronic acid	Hyaluronic acid facilitates wound healing cascade in all stages including inflammation, reepithelization, granulation tissue formation, proliferation, and remodeling.	High swelling ratio and water uptake, non-immunogenic and biodegradable	Films, injectable scaffolds, sponges, Hydrogels	[204]
Keratin	Keratin activates SCs, which is beneficial to repair the nerve. It also inhibits microbial burden.	Proper aeration, and exchange of the wound fluid/ exudates.	Films, dermal patches	[205]
Pectin	Anti-inflammatory properties (due to the esters and galacturonic acid) and suppression of the enzyme i.e., COX-2 and iNOS are possible with pectin. Functionalized pectin shows anti-thrombogenic effects.	Biodegradable, biocompatible.	Films, Hydrogel	[206]

main groups, including articular (hyaline), fibro, and elastic. Heterotypic collagen fibrils and proteoglycan–glycosaminoglycan webs of aggrecan and hyaluronan are the main components of cartilage ECM. As a wear-resistant and flexible tissue, hyaline is present within the joint to carry and distribute the load. Cartilages of the larynx, ear, and epiglottis are more elastic than the hyaline. Fibrocartilage as an inflexible one is present in the knee between the vertebrae. Limited cartilage restoration is attributed to blood vessels and neural system shortage in cartilage tissues, resulting in rheumatoid arthritis, inflammatory disease, and joint deterioration. Collagen II and hyaluronan are the main elements of cartilage ECM. Cartilage injuries are associated with ECM degradation and recruitment of joint chondrocytes from near areas with reduced infiltrations and inflammatory cell vascularization [251,252].

Biopolymers applied practically for cartilage tissue engineering are summarized in Table 8. According to this table, various types of scaffolds can be used in cartilage regeneration. However, signal paths and biological signs should be considered in cartilage regeneration. Several factors are involved in chondrogenesis including transforming GF β (TGFβ), parathyroid hormone-related protein (PTHrP), Wnts, Indian hedgehog, thyroid hormone, bone morphogenetic protein (BMP) superfamily, platelet-derived factors (PDGFs), insulin-like GFs (IGFs),

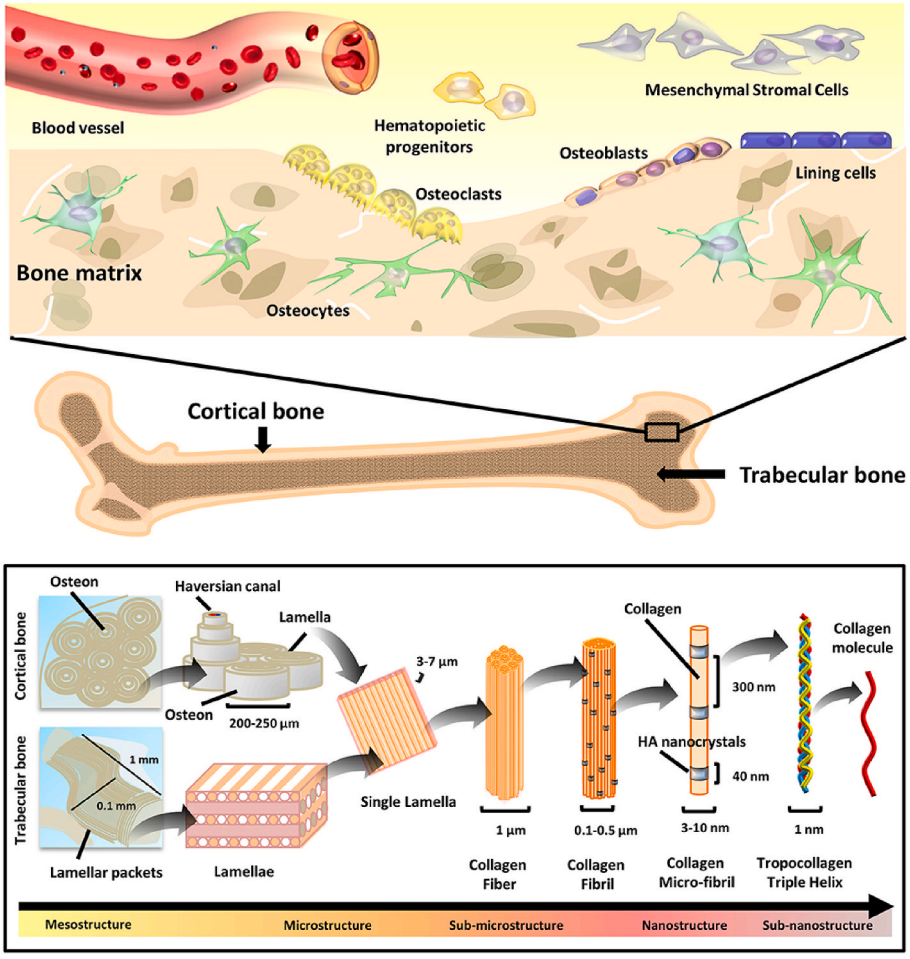

Fig. 9. Bone tissue structure: (top) bone cells, and (bottom) bone structure. The different structural elements are represented, ranging from the mesostructures (i.e., osteons/lamellar packets) to the sub-nanostructures (i.e., collagen molecule). Reprinted with permission from Ref. [218].

Table 7
Biopolymer/CaP green composites or biocomposites together with the type of biopolymer and resulting platform, and also their fabrication route.

Incorporation procedure	Biopolymer	platform type	Fabrication route	Ref.
Physically incorporation	Collagen	Porous scaffold, Nanofibrous	Freeze-drying after the crosslinking of collagen/HAp mixture, using the Electrospinning method polyvinyl alcohol was added to achieve the better electrospun mat	[234–236]
	Chitosan	Porous, Macroporous, scaffold	Freeze-drying the chitosan–nHAp Dispersion	[237]
	Gelatin	Porous scaffold	Crosslinking after lyophilization	[238]
	Alginate	Porous scaffold	Gelation occurred by releasing the calcium ions from HAp, Salt leaching	[239]
	Silk	Knitted scaffolds	Silk was soaked in HAp slurry followed by freeze-drying	[240]
Chemical deposition	Collagen	Sponge; fibrous scaffold	Immediate titration precipitation technique	[241]
	Chitosan	Scaffold	Double-diffusion method to create nHAp followed by freeze-drying	[242]
	Silk	Micro-porous scaffold	Silk was soaked in $CaCl_2$ and Na_2HPO_4 solution	[243]
	Alginate	Beads	Soaking the Na-alginate solution including phosphate into the calcium including gelling bath	[244]
Biomimetic mineralization	Collagen	Hydrogels, Fibrous, unidirectional lamellar structure	Mineralized enzymatically by the inclusion of alkaline phosphatase, Biomimetic hierarchical nanoapatite assembly using polyvinylphosphonic acid as a biomimetic analog of matrix phosphoproteins, inclusion of SF-derived polypeptide to emulate the character of anionic non-collagenous proteins in mineralization procedure	[245]
	Chitosan	Porous scaffold	Nanocrystals stimulate the biomineralization process	[246]
	Alginate	Porous scaffold	Incubating in an SBF solution	[247]
	Collagen/ Chitosan	Hydrogel	Utilizing modified culture media to increase the mineralization	[248]
	Cellulose	Pellicles/tubes	Functionalized by carboxymethyl group as a negative spot to start the nucleation.	[249]

fibroblast GFs (FGFs), and various vitamins [253,254]. TGFβs synchronize chondrocyte proliferation differentiation, and induces the expressions of RY-box, resulting in collagen II and aggrecan formation. Wnt and β-catenin-dependent signaling play important roles in improving chondrocytes. The β-catenin-dependent pathway promotes endochondral ossification and axial growth [255].

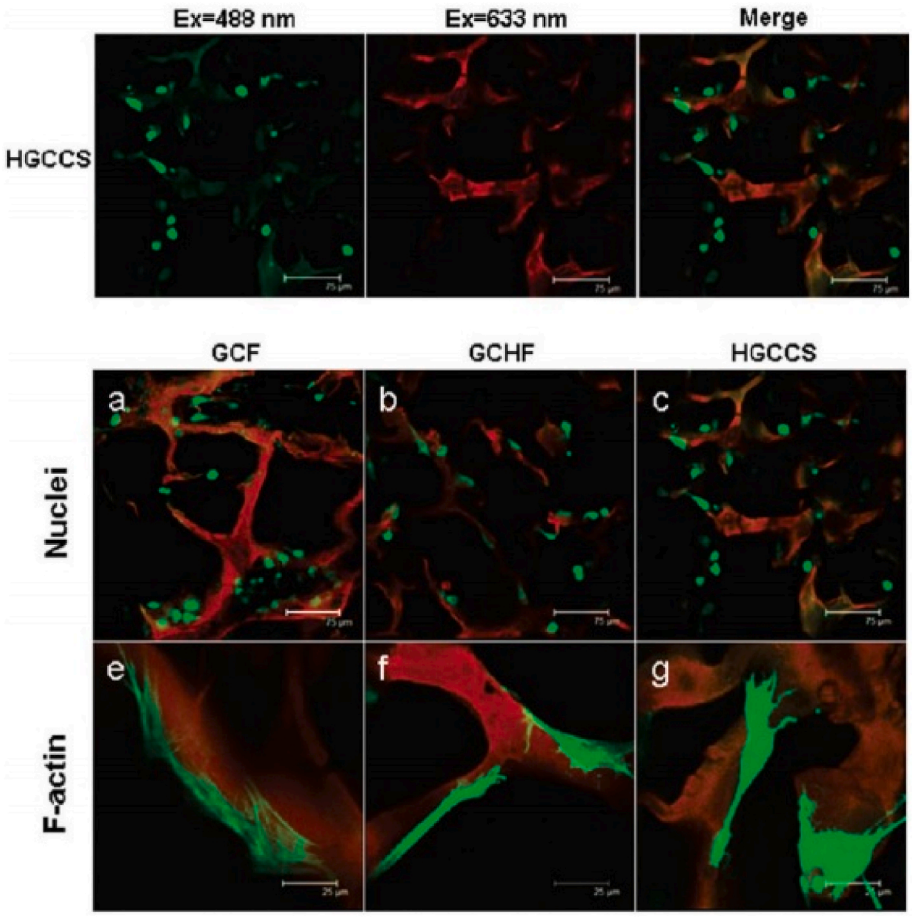

Fig. 10. Confocal images of the actin cytoskeleton organization of the BMSCs cultured of a rat after three days of treatment on the genipin- and chitosan-based framework (a and e); on the genipin- and chitosan-reinforced with HAp framework (b and f); on the HAp-based genipin-conjugated chitosan scaffold (c and g). These images were taken after acridine orange and Alexa Fluor nuclei and F-actin staining. Reproduced with permission from Ref. [233]. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 8
Biopolymers applied for cartilage tissue engineering, together with fabrication route, structural shape, and biological responses.

Biopolymer	Fabrication method	Structure	Biological assessments	Ref.
Collagen	Phase separation, Temperature variation	Random, Oriented	Good MCSs proliferation, oriented scaffold acted better than random. Along with SDF-1 encourages osteochondral repair by simplifying cell homing	[256]
Gelatin	Electrospinning	Nanofibers	enhance spreading, proliferation, and attachment of chondrocytes	[257]
Fibrin	Gelation	Hydrogel	Can be easily functionalized using ECM which induces the cartilage repair	[258]
Agarose	Self-gelling	Hydrogel	stabilize the chondrocyte phenotype and increase the proteoglycan and precipitation of the glycosaminoglycans	[250]
Cellulose	Gelation	Hydrogel	proper development of new cartilage along with ECM elements like collagen and glycosaminoglycan	[259]
Alginate	Gelation	Hydrogel	Collagen II and Sox-9 expression increased later than one-month post-differentiation, Development of ectopic cartilage healing within and around the implanted region	[260]
Chitosan	Gelation	Hydrogel	Higher spreading of cells, appropriate regeneration of defected cartilage by scaffolds implanting after 6 months, no inflammation was observed later than implanting allogenic chondrocytes	[261]
Elastin	–	Hydrogel	Increased Hyaluronic acid formation, enhanced cartilage gene markers expression, increased sGAG deposition and decreased undesired fibrocartilage phenotype	[262]

Compared to scaffold-free methods, cartilage regeneration using biopolymers has many advantages, including proper filling of the damaged site, low difficulties at donor sites, few implantation-associated challenges, and accelerated healing. Furthermore, fabricating a 3D scaffold suppresses chondrocyte dedifferentiation and enhances the synthesis of hyaline-like cartilage. An effective cartilage-based tissue construction produces liquid and solid phases of the connective tissue, biomimetic zone, and regional cartilage structures that integrate with underlying native tissues. Therefore, proper biomaterials should be selected in order to facilitate cartilage regeneration. Suitable substrates for efficient tissue regeneration should mimic normal tissue properties. Collagen II and glycosaminoglycan (GAG) play a vital role in maintaining chondrocytic phenotypes and chondrogenesis stimulation. Otherwise, chondrocytes de-differentiate or produce fibrocartilaginous matrices enriched with collagen I that cause failure in hyaline formation. Table 8 suggest that blending biopolymers together or with a sustainable complement among nano-scale bio-based materials would be a solution in view of sustainability perspective.

5. Conclusion and future direction

In clinical settings, tissue engineering is bast known for its ability to improve the life quality of patients by providing the damaged organ with the possibility of repair through functional contructs. Therefore, designing biomaterials with the required biocompatibility and tissue-mimic performances has attracted significant attention over the last

decades. Since characteristics of biomaterials are limited to their mechanical strength, degree of biocompatibility, and ability to mimicking native ECM architecture, there has been need for blending biomaterials together of incorporation of reinforcing agents to biomaterilas. Biopolymers are similalrly reinfirced with the secondary biopolymer as the complement to the original one, or amalgamation of additives, particulalrly nanomaterials. Green polymer composites or briefly saying biocomposites are a class of complex biopolymers which intengrate several fucntions into one biomaterial. They can be categorized based on their source, including biopolymers derived from agro-resources, micro-organisms, and biotechnology. Due to their proper biocompatibility and tunable properties, biocomposites of polymers exhibit acceptable performances in tissue engineering and repair. Bearing in mind the importance and popularity of 3D and 4D printing machines nowadays, the importance of biocomposites is obvious to experts working in the filed. However, the complexity of biomaterials used for tissue repair necessitates designing multifucntional composite biopolymer composites mimicking tissue and organ behavior. In this sense, different strategies have been developed to rely on requirements of tissue engineering with the aid of advanced biocomposites. For instance, conductive materials have been added to biopolymer matrices in neural tissue engineering to endow conductivity to biopolymers. Biocomposites are expected to play a more key role in the development of multifunctional scaffolds for tissue engineering and regenerative medicine in the future. This contribution provides support for future developments of biocomposites, considering that biopolymers quilified for tissue engineering, together with their cellular interactions, properties, advantages and limitations are comprehensively reviewed and their mechanisms of action are discussed. Classification of sustainable composites targeted at regenerative medicine and tissue engineering necessitates availability of adequate data, statistics, and more critically reliable reports, which seems to be a hot ongoing debate between materials scientists and biomedical engineers. Moreover, contiribution of machine learning algorithms in designing and fabricating intelligent biocomposites should specifically be considered.

Authors' contribution

P.Z.: Writing the first draft; F.S.: Supervision, Editing and revision of the final version; M.Y.A., M.K.Y., and A.E.: Investigation, Formal analysis; M.B., N.P.S.C., and N.R.: Methodology, Formal analysis, Graphics; T.K.: Supervision; J.K-L.: Editing the final version; M.R.S. and M.M.: Conceptualization, Supervision, Editing and revision of the final version.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

This is a review article.

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