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REVIEW

Recent Advancement of Biopolymers and Their Potential Biomedical Applications

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Abstract

Recently, the advantages of biopolymers over conventional plastic polymers are unprecedented, provided that they are used in situations in which they raise the functionality and generate extra benefits for human life. Therefore, biopolymers have received much attention because they play an important place in day-to-day life for their specific tunable characteristics, making them attractive in a wide range of applications. Biopolymers can produce materials with tunable properties such as biodegradability, biocompatibility, renewability, inexpensiveness, availability, which are critically important for designing materials for use in biomedical applications. In addition to these properties, smart biopolymers could be prepared by changing the polymer components, which would create more target oriented applications. Therefore, this review interprets how biopolymers and their various forms can be potentially used in biomedical applications, including drug delivery, infections, tissue engineering, wound healings, and other as wells. Special emphasis will be provided on the applications of biopolymers in the field of drug delivery, tissue engineering, infections, and wound healing, which indicate the advancement and employment of the various biopolymers in recent biomedical applications.

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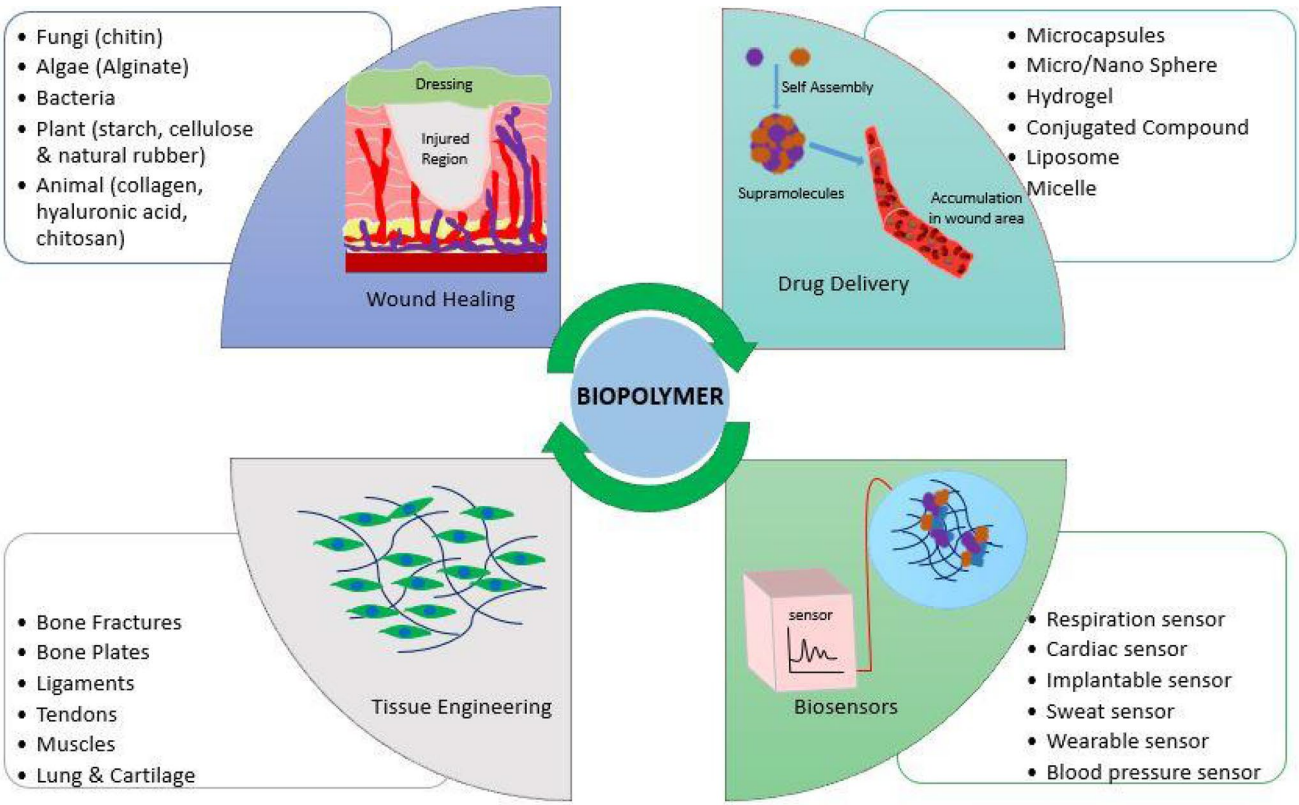
Graphical abstract



Keywords Biopolymers · Drug delivery · Tissue engineering · Scaffolds · Wound healing · Sensors · Hygiene

Introduction

Biopolymers derived from renewable sources are abundant in nature, biocompatible, inexpensive, and degradable without leaving any toxic residues, which prime characteristics of biopolymers to be an ideal candidate for biomedical applications [1, 2]. Due to their biodegradability and nontoxicity, biopolymers attained much attention used in liver and cardiac tissue engineering and wound healing as hydrogel, powder, and films in tissue engineering [3–5]. Natural bioorganisms such as bacteria, fungi, algae, etc. help to promote the degradation or break down via aerobic or anaerobic processes into small molecules leaving behind some organic by-products such as CO_2, H_2O, etc. [1]. Besides their excellent attributes, the structures of biopolymers resemble the structure of extracellular matrix (ECM) macromolecules which allow them to be compatible and functional appropriately within the host. Natural polymers include chitosan, starch, carrageenan, agar, alginate, etc. from plant carbohydrates and whey protein, soy protein, gluten, collagen, zein, casein, gelatin, etc., from plant or animal protein origin. These polymers have been used vastly in drug delivery, such as encapsulation, solid monolithic matrix systems, beads, microparticles, scaffolds, nanoparticles, as well as inhalations and injectable systems and viscous liquid formulations [6–8]. The polymeric material plays the role as matrix or drug release modifiers, viscosity modifiers, binding agents, film coating substances, disintegrating agents, solubilizing agents, emulsifying agents, suspending agents, gelling agents, and bioadhesives [9]. Biodegradable polymers derived from starch are suitable for drug delivery in the form of the microcapsule, microsphere, implants, or hydrogel. It does not require any surgery to remove the device after drug depletion [10]. Synthetic biopolymers include poly(L-lactic acid) (PLA), poly(e-caprolactone) (PCL), poly(glycolic acid) (PGA), poly(vinyl alcohol) (PVA), poly(butylene succinate) (PBS), etc. are also garnered much attention in biomedical fields [5]. And finally, biopolymers produced through microbial fermentation include microbial polyesters, such as poly(3-hydroxybutyrate-co-3-hydroxyvalerate) (PBHV), poly(hydroxyalkanoates) (PHAs), poly(β-hydrocxybutyrate) (PHB), etc., and microbial polysaccharides including curdlan and pullulan are also applied for biomedical applications. Synthetic biodegradable polymers

like poly(α-hydroxyesters), polyanhydrides, and polyorthoesters, have found more versatile and diverse biomedical applications owing to their tailorable designs or modifications and extensively used for fabricating tissue engineering matrices [11]. Biopolymer-based scaffolds can regenerate damaged tissue and organs in the host body and promote healing tissue regeneration process. These scaffolds have drawn much attention for engineering tissues such as skin, cartilage, vascular, bones etc., as they offer suitable conditions for the tissues, cells, and organs to disintegrate and proliferate effectively [12–15]. The scaffold should meet some essential criteria to be a promising candidate for biomedical application such as biocompatibility, biodegradability, nontoxicity, non-inflammatory, nonimmunogenic, structural integrity, optimal porosity, sound mechanical and physiological properties [8, 14, 16, 17]. During the regeneration process, the scaffolds serve as an alternative three-dimensional structure of ECM and allow an appropriate environment for tissue regeneration. Application of biopolymer-based scaffolds would be helpful to minimize some unavoidable side effects of non-biocompatible polymers' implants, such as chronic inflammation, immunological activity, and toxicity within the body.

Recent advances in modern biotechnology regarding cell regeneration with the aid of signal molecules are promising techniques in biomedical applications. Smart biomaterial research has triggered the necessity to develop smart biopolymer scaffolds for biomedical applications. For the breakthrough in the biomedical field, this review focuses on the background and recent advances of natural-based biopolymer scaffolds' application in the following sections: (1) drug delivery, (2) tissue engineering, (3) wound healing, and finally, both natural and synthetic in (4) miscellaneous biomedical applications. Special emphasis has been given to the applications of biopolymers in drug delivery, tissue engineering, infections, and wound healing applications, which indicate the advancement and employment of the various biopolymers in recent biomedical applications. Lastly, this review addresses some recent challenges which need to be considered to make existing scaffolds more useful in future applications.

Classification and Attributes of Biopolymers

Depending on the origin of raw materials (extracted from natural resources such as starch, sugar, cellulose, and fossil oil), biopolymers can be categorized into three broad groups such as (1) natural, (2) synthetic, and (3) microorganism-based biopolymers [1, 18]. The natural resources of producing biopolymers comprise microorganisms, plants, and animal tissues and can also synthesize from aerial, terrestrial, and marine living organisms. For example, microorganisms such as bacteria, fungi, yeasts, molds, smuts, and many other forms of what a primitive life is can be very potential to offer an enormous variety of polymeric biomolecules with outstanding structural and biochemical attributes. These biopolymers comprise polysaccharides such as cellulose, chitin, chitosan, dextran, chitin, hyaluronic acid, etc., and proteins like silk, keratin, etc. Plants have been a precious and renewable source of both polysaccharides and proteins for a long time. Animals are also a potential source, whether highly developed or not, whether they live on the land, sea, or air can provide natural structures with strong potential in the biomedical field. Examples of these structures comprise glycosaminoglycans (chitin, hyaluronic acid, etc.), proteoglycans, and proteins (collagen, elastin, gelatin, etc.) with the addition of deoxyribonucleic acid, the genetic material instigated from all living sources [19].

Based on the monomeric unit present and the structure, natural biopolymers can be classified into three types: polynucleotides, polypeptides (proteins), and polysaccharides [19–21]. The nucleic acid is a generic biological material consisting of a large number of molecules in sequence. These are polymers having nucleotides as monomer units. There are two types of nucleic acids, DNA and RNA. These are linear polymers having smaller molecules (monomers unit) attached in sequence. Several nucleotides are linearly linked by covalent bonds to form polynucleotides. A nucleotide molecule is composed of three distinct molecules: five-carbon sugar, a phosphate group, and a nitrogenous base, as shown in Fig. 1. In DNA and RNA polynucleotide biopolymer, a nucleotide monomer has a phosphate group and bonded to the sugar of the next nucleotide monomer, making a chain having a regular sugar-phosphate group [22]. In DNA, the sugar molecule is deoxyribose, but in RNA, it is ribose. Also, DNA biopolymer usually has a double-stranded chain, whereas RNA has linear chains of α-amino acids. A combination of polypeptide molecules results in the formation of proteins [19]. The amino acids are covalently bonded with the help of peptide bonds. The individual amino acid linked in the protein chain is called a residue, and the linked

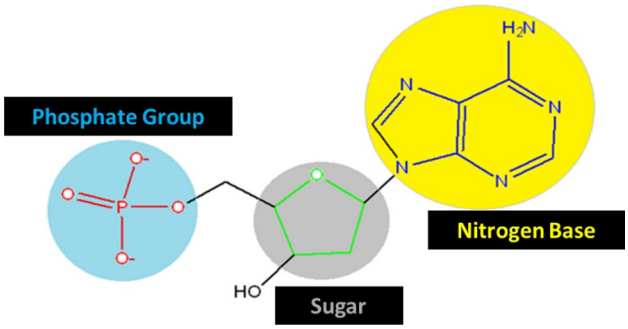


Fig. 1 A nucleotide monomer showing phosphate, sugar, and nitrogenous base group

chain of nitrogen, oxygen, and carbon is called the protein backbone (Fig. 2). The picture shows how three amino acids are linked by peptide bonds forming polypeptides.

Proteins can be extracted from a wide variety of materials, including wool, leather, silk, gelatin, and collagen. Differ in the sequence of amino acids make a lot of varieties of proteins. Proteins have essential roles in living organisms include immune responses, cell adhesion, and cell signaling. Polysaccharides are long chains (linear or branched) of monosaccharide units bonded together by glycosidic linkages, but upon hydrolysis release the constituent of monosaccharides or oligosaccharides. Examples of polysaccharides include storage polysaccharides such as starch and glycogen and structural polysaccharides such as cellulose and chitin [20]. Pattanashetti et al. explained the smart biopolymeric materials, which have the property to respond to significant changes due to small changes in the environment. They referred to them in the category of environmentally sensitive polymers. They classified smart biopolymers into three categories: pH-sensitive smart biopolymers, thermosensitive smart biopolymers, and stimuli-responsive biopolymers [20].

Riedel et al. classified biopolymers into three categories—polymer chain, polymer, and monomer [23]. Polymer chain biopolymers are naturally synthesized polymers such as carbohydrates, proteins, polyphenol resin, etc. Polymer category biopolymers are biotechnologically synthesized polymers like polyhydroxybutyrate and copolyesters. The third type is naturally synthesizing monomer unit polymers such as plant oil and derivatives from sugar. Rebelo et al. classified the biopolymers into four categories, as mentioned in Table 1.

Recent technological advancement enables the vast application of biopolymers in the medical field and can be categorized into drug delivery applications, wound dressing and healing materials, tissue engineering, biomedical sensors, surgical scaffolds, etc. Controllable drug release in our bodies can be accomplished easily using biodegradable polymer encapsulation. In wound healing, highly biocompatible nonwovens can be used to replace human tissue and simple sutures, staples, clips, or meshes are also available. Most of the biopolymers exhibit good film-forming behaviors, making them appropriate in high-performance applications and in traditional commodity uses. Biopolymer based nonwovens can also be used in agriculture, filtration, hygiene, and protective clothing.

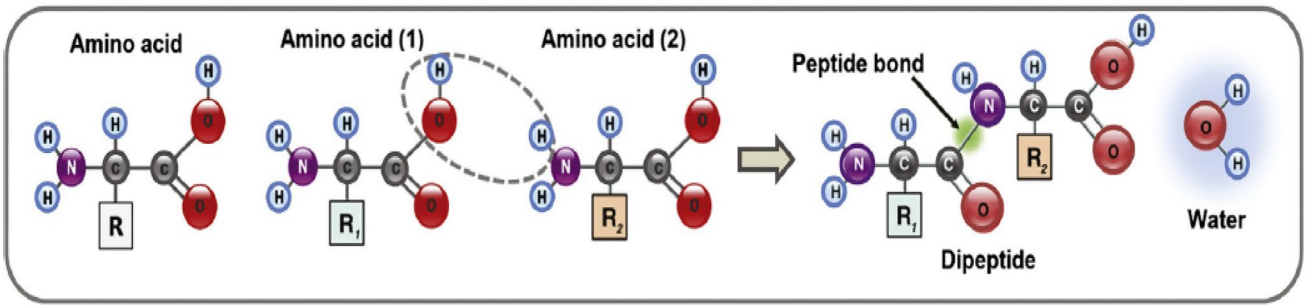


Fig. 2 Structure of protein. Reprinted with permission [19]

Table 1 Classification of biopolymers [21]

Classification	Origin	Biopolymers
Polysaccharides	Plant/algal	Starch, cellulose, agar, alginate, pectin, various gums, carrageenan,
	Animal	Chitin/chitosan, hyaluronic acid
	Bacterial	Xanthan, dextran, gelian, levan, curdian, polygalactosamine, cellulose (bacterial)
	Fungal	pullulan, elsinan, yeast glucans
	Lipids/surfactants	Acetoglycerides, waxes, surfactants, Emulsan
Proteins		Silks, collagen/gelatin, elastin, resilin, adhesives, polyamino acids, soy, zein, wheat gluten, casein, serum albumin
Polyesters		Polyhydroxyalkanoates, polylactic acid
Specialty polymers		Shellac, poly-gamma-glutamic acid, natural rubber, synthetic polymers from natural fats and oils, nylon from castor oil

Promising Areas of Biopolymer Applications

Biopolymers play versatile roles in various functionalities in the human body such as embrace cells to form tissues and provide signals to the cells to control their behavior. They also moderate the skin's hydration and elasticity to maintain a natural environment. They make all joints and gastrointestinal tracts flexible via lubrication and protect from pathogens through accumulating into the mucus gel which covers human eyes and respiratory tract [20]. In addition, biopolymer-based scaffolds do a lot of works such as signal transportation to monitor cell behavior, maintaining skin's hydration and pliability, protecting from pathogens and maintaining joints flexibility through lubrication etc. This section discusses the promising application areas of biopolymers and their composites with challenges, state-of-the-art methods, and innovation in carriers.

Drug Delivery

The controlled release of a therapeutic agent in a tunable dose is the most fundamental requirement for any drug delivery system that can be accomplished with a successful conjugation between a therapeutic agent and a drug delivery vehicle [9, 24–27]. However, the coupling of a drug with a delivery agent depends on the chemical structure (that can be both hydrophilic or hydrophobic) of the drug molecules; hence, rational design of a drug delivery agent must be required for a successful conjugation [26, 28, 29]. Furthermore, the drug carrier must inhibit any enzymatic degradation of a therapeutic agent before its controlled release. After a successful delivery, the drug carrier must be possessed non-toxicity, biodegradability, and most importantly, it should release from the body without any side effect [9, 30, 31]. In general, polymeric materials are an excellent candidate for acting as a drug delivery agent. However, bio-polymer and its derivative showed better properties such as ease of functionality, water-solubility, non-toxicity, biodegradability, and biocompatibility [21, 32]. Moreover, these biopolymers can reduce drug toxicity with a controlled drug release. They also reduce any enzymatic degradation before releasing a therapeutic agent in the target sites. Releasing of therapeutic agent can be triggered by various stimuli such as physical (sonophoresis, temperature, light, magnetic or electric field), chemical (biochemical, hypoxia or pH), environmental or combination of more than one stimulus (as shown in Fig. 3). In this context, biopolymers are promising materials as drug delivery agents. Polysaccharides, polypeptides, and proteins are three major classes of biopolymers that are extensively using as drug delivery systems.

Carbohydrate molecules consist of long-chain monosaccharide or disaccharide unit covalently linked with glycosidic linkage are known as a polysaccharide. Plants (starch, hemicellulose, cellulose, agar, glucomannan, pectin, guar gum, and gum acacia), microbes (curdlan, gellan, dextran, xanthan), algae (alginate, carrageenan), and fungae (chitin, pullulan, scleroglucan) are the major source of polysaccharide [33–36]. Most of them are neutral or possess a negative surface charge. Only chitin can have cationic polysaccharides. However, functionality is one of the major advantages of polysaccharide molecules, which can control the overall drug delivery systems. Different types of drug vehicle systems such as micro/nanocapsules, micro/nanosphere, polymer-drug conjugation, micelle, liposome or hydrogel formation are the most common drug delivery system where therapeutic agents must disperse or encapsulate in the biopolymer matrix [37–40].

Chitosan (CH), prepared via N-deacetylation of chitin, is the only cationic polysaccharide that is most widely used in different types of drug delivery systems [41–45]. Nowadays, CH can be successfully used in the oral, vaginal, nasal, parental, or injectable route. It is well known that CH is compatible with living tissue; hence it must reduce enzymatic degradation. It is also reported that drug diffusion from the chitosan matrix can be controlled for tunable doses. Moreover, drug absorption and stabilization in the polymer matrix are other advantages for chitosan-based drug delivery systems [46]. Chitosan-drug conjugation is one of the most successful drug delivery systems where different types of chitosan molecular weight were used for this conjugation formation and cleaving condition can be pH or GSH (glutathione) sensitive based on the drug types [46, 47]. Hydrogel formation with chitosan is another approach for any sensitive protein or gene delivery [44, 48, 49]. Because some genes or proteins are susceptible to be damaged in contact with organic solvents or body fluids. Therefore, the cationic chitosan can form hydrogel with the presence of polyanion such as tripolyphosphate (TPP); hence, strong ionic crosslinking can form strong gelation that can protect genes or proteins till the controlled drug released in the target active sites [50–52].

Cellulose is the most abundant biopolymer with excellent mechanical and biological properties such as biocompatibility, biodegradability, and low cytotoxicity [53]. Cellulose with different aspect ratios such as microcrystalline cellulose (MCC), cellulose nanomaterials (CNC and CNF) and bacterial nanocellulose (BNC) are common classes of materials that are excellent candidates for drug delivery systems [54–57]. However, bacterial nanocellulose (BNC) is the most promising material compared to other types of cellulose due to its excellent biocompatibility with different

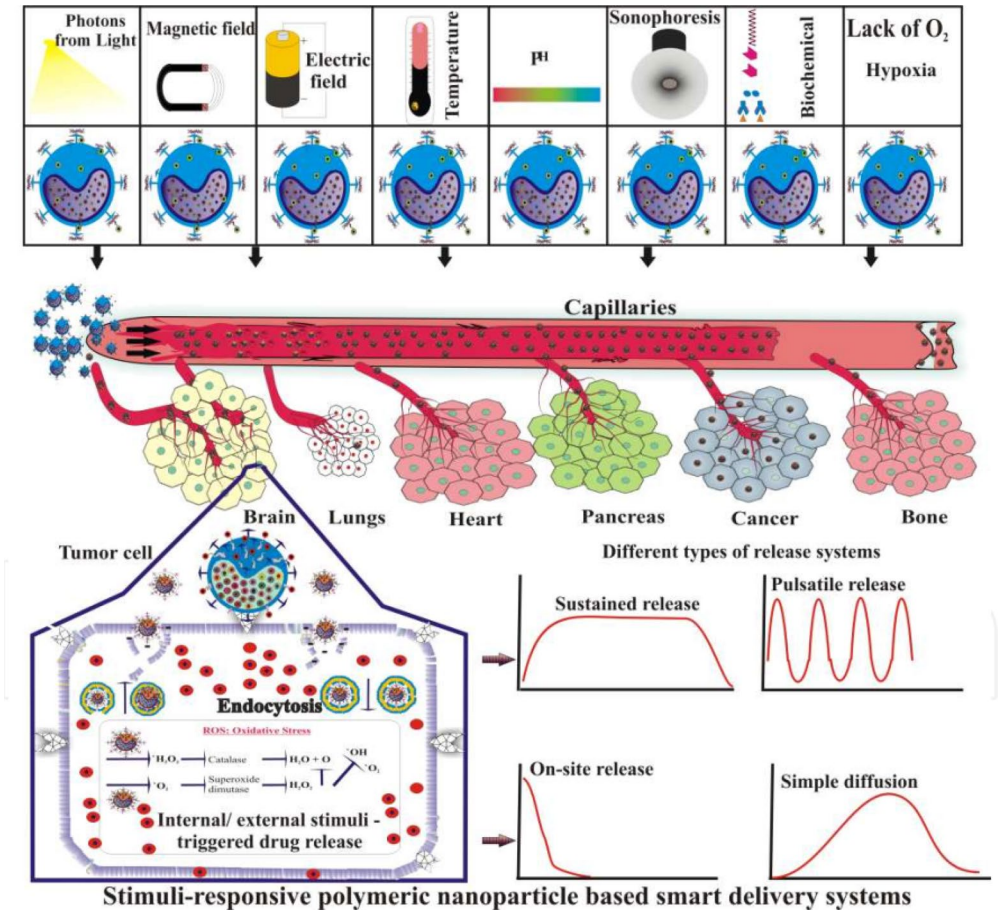


Fig. 3 Controlled therapeutic agent release based on different stimuli-response triggered by the physical, chemical, or environmental process. In general, external stimuli can be dominated by physical processes such as light, sound, heat, magnetic, or electric fields. Stimuli-responsive functional groups or grafting of nanoparticles on the polymeric system are commonly employed for external stimuli. Chemical or environmental processes are usually used for internal stimuli with pH, hypoxia, and selective functional groups (responsive to a specific biochemical process of the body system) of the polymeric system. Reprinted with permission [221]

shapes (such as spheres, tubes, fibrous, aggregates, fleeces, or foils) that can be controlled with its biosynthesis route. Moreover, without showing any severe signs of inflammation or toxic response at the cellular level, in vivo or in vitro biocompatibility of BNC can up to 1 year compared to other types of cellulose systems [58]. Chemical modification such as etherification, esterification, phosphorylation, or amidation is commonly applied in BNC for incorporating any diffusion barrier, which significantly modifies the drug release rate [56, 59–62].

Collagen is the most abundant protein from the animal kingdom that consists of a triple helical structure of glycine–proline–hydroxyproline repeating unit. Due to their excellent biocompatibility, it has been using in drug delivery application as microparticle, coating, films, or hydrogels [63–67]. Denatured collagen (gelatin), as well as collagen with a binding protein, can deliver therapeutic agents ranging from small molecules to biomacromolecules (DNA, protein, or even cells). Sometimes collagen might combine with liposomes where a therapeutic agent must be encapsulated inside the liposomes. This collagen with the liposomes approach may improve both drug release rate and therapeutic efficiency. Collagen corneal shields, contact lenses known as BioCora collagen shields, also have potential applications for water-based conjunctival antibiotics and corticosteroids such as Vancomycin, Amphotericin-B, pilocarpine, Gentamycin, bacterial and HSV keratitis [67–69].

Grafting of smart polymers on the biopolymer surface or biopolymer composites is also using for drug delivery systems [70, 71]. Drug diffusion rate, inhibition of enzymatic degradation, altering the pH-responsive range or hydrogel formation is commonly achieved with the composite systems [72, 73]. Grafted BNC-g-poly (acrylic acid) hydrogels showed extended pH-responsive drug delivery compared to the pristine BNC system due to changes in surface chemistry [74]. Composite hydrogel system such as alginate in BNC scaffolds demonstrates a prolonged drug release rate due to intermolecular drug-drug interactions [74, 75].

Tissue Engineering Applications

Tissue engineering is the most attractive approach that deals with repairing and regenerating biological tissues substituting by biopolymer composites implants. One of the prime requirements of biopolymer composites to be an ideal scaffold in tissue engineering and regenerative medicine is mimicking the collagen-rich extracellular matrix (ECM) that supports the structural and biochemical. The classical cell culture, growth and proliferation can be enhanced by mimicking the physical and biochemical nature of tissues in vivo by reconstructing the original structure of ECM applying scaffolds having similar surface topography.

Hard Tissue Scaffolds

In tissue engineering, necessity of hard tissue scaffolding is raising for different medical application such as bone fractures and cartilage [76–78], imperfections [79], joint replacements [80, 81], bone plates, bone cement [82], artificial ligaments [83], and tendons [84–87] & dental implants [88]. Human bone is a complex ordered tissue having ~ 69% hydroxyapatite (HAP) (bio-ceramics), ~ 21% collagen (natural polymer), 9% moisture, and 1% other ingredients [89]. The human bone is a complex bio-composite structure, called the ECM (Fig. 4) associated with the musculoskeletal system of the body. The healing process of an injured bio-composite system is linked to a lot of factors such as the regeneration of the tissue, biocompatibility, low toxicity, bio-absorbability, bio-mineralization, and maintaining suitable mechanical strength [90–92]. Now biomaterials such as protein (collagen) and polysaccharides (chitosan, silk, alginate, starch, and bacterial cellulose) are used with hydroxyapatite to generate a functional bio-composite anticipated to regenerate the natural tissues with proper biomechanical performance, including biomineralization.

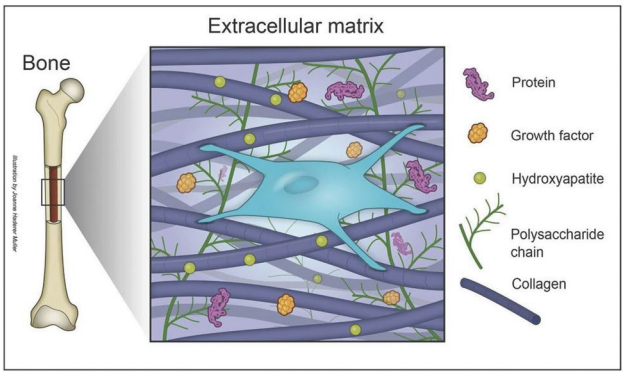


Fig. 4 Extracellular matrix (ECM) of human bone. Reprinted with permission [222]

Collagen is the most abundant, most studied, and critical structural protein found in the ECM of vertebrate tissues. Collagen is a triple-helical structure of a large protein that formulated an essential part of natural tissue scaffolds in mammals [93]. Recently, several studies have been performed and exploited on the collagen-based composite to regenerate bone tissue [94, 95]. In Fig. 5, an example of collagen/HAP composite obtained from O'Brien's literature [96] confirming the successfully incorporated collagen protein into the HAP matrix.

Table 2 shows the structural properties and biocompatibility of collagen/HAP composite that are summarized from literature with varying % of HAP.

Both native [97–99] and modified collagen [100, 101] are used in several studies with HAP [102] for bone tissue regeneration. Apart from collagen, other biopolymers such as chitosan [103, 104], silk fibroin [105], alginate [106], starch [107], bacterial cellulose [108], and cross-linked cellulose nanocrystal (CNC) aerogels [109] are also used as a natural polymer with hydroxyapatite filler. All these

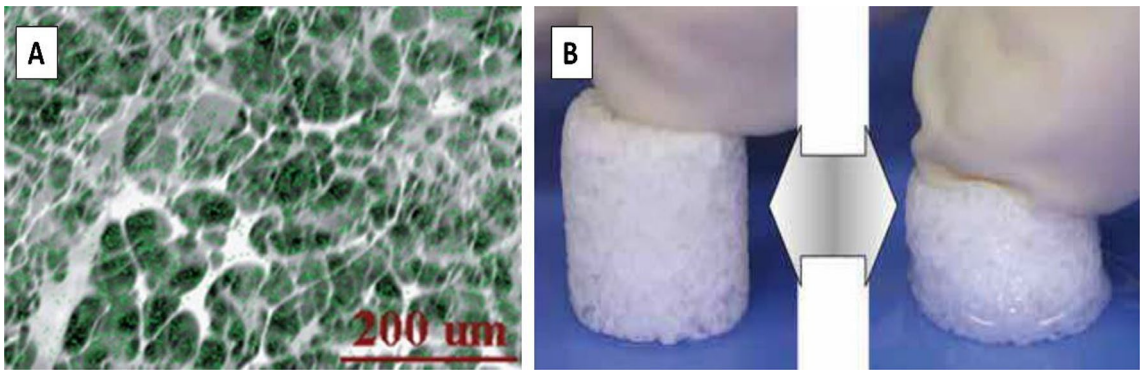


Fig. 5 **A** Composite of the collagen-HAP scaffold with uniform distribution of HAP particles (Green) [96] **B** flexible collagen-HAP viscoelastic composite [223], Reprinted with permission Gleeson et al. [110] reported that collagen/(0–200 wt%) HAP composite could attain better biocompatibility, cell-mediated mineralization (0.01–0.2) including biomechanical performance (0.4–1.4 kPa) (Color figure online)

Table 2 Structural properties and biocompatibility of collagen/wt% HAP (X)

Collagen/wt% HAP (X)		Compressive stress (KPa)	Permeability (m^4/Ns)	Cell-mediated mineralization (28 days)	Cell no after 28 days (millions)
X	0 [110]	0.39	4.86E-10	0.029	–
	20 [111]	2.5 E06 (Nanoindentation)	–	–	–
	30 [112]	2.29	–	–	–
	50 [110]	0.49	2.38E-09	0.017	1
	80 [112]	1.82	–	–	–
	100 [110]	0.86	4.05E-09	0.023	1.25
	200 [110]	1.25	4.83E-09	0.097	0.55
	~[113]	0.9	–	–	–

biopolymers are well studied for both biocompatibility and mechanical response for particular applications. In Fig. 6, the HAP composite containing different biopolymer are summarized. As seen from Fig. 5, the composite structures are mostly porous structures which are required for the biocompatibility and bio-regeneration process. Moreover, optimized mechanical properties are also obtained through the HAP filler effect. The main drawback of biopolymer has a lower mechanical response, and on the other hand, the only HAP can hinder the bio-regeneration process. It is possible to overcome this problem using different optimized biopolymer composite to regenerate the bone tissue [96].

Soft Tissue Scaffolds

The second category of biological tissue substitution deals with soft tissue scaffolds application. Neural tissues are mainly known as the soft tissues having stiffness values 0.1–1 kPa for brain parts and 230 kPa for the spinal cord [114, 115]. It includes nerves, muscles, ligaments, tendons, skin, blood vessels, lungs, cartilage, intervertebral discs,

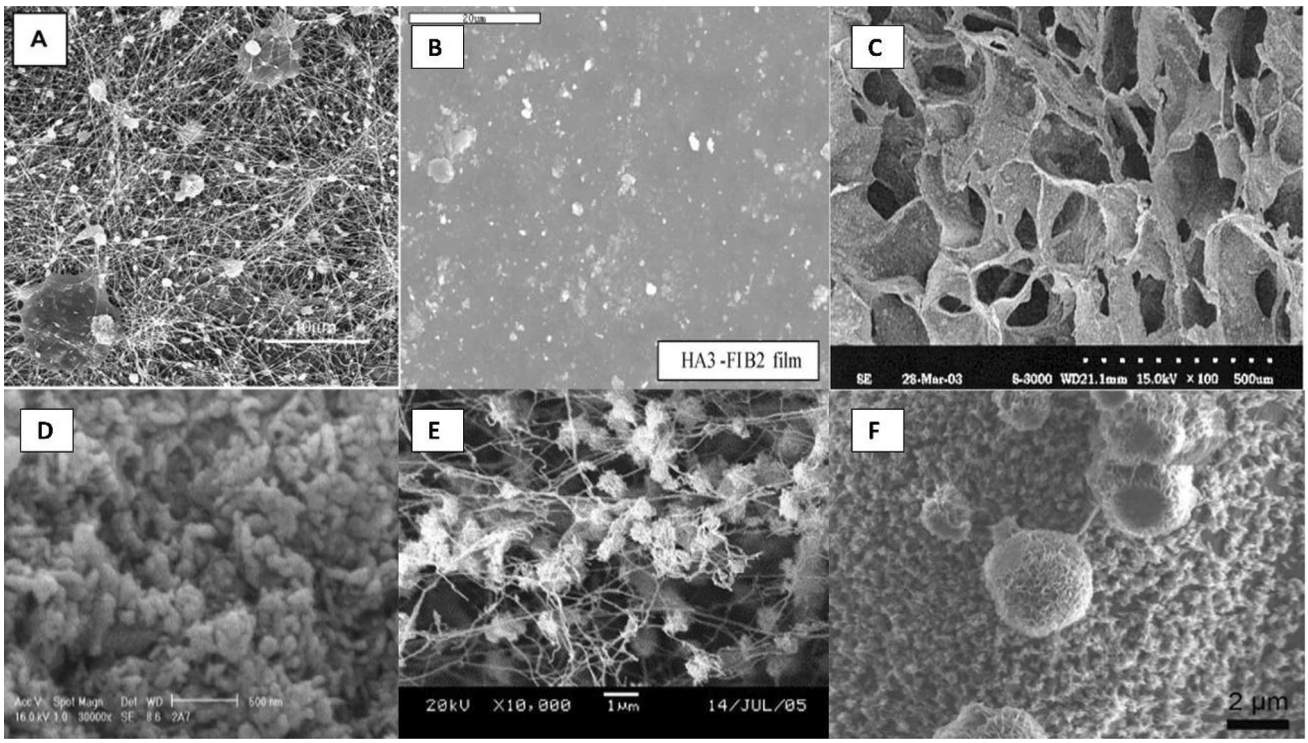


Fig. 6 SEM micrograph of biopolymer-based HAP composite for hard tissue regeneration containing **A** chitosan [103], **B** silk fibroin [105], **C** alginate [106], **D** starch [107], **E** bacterial cellolose [108] and **F** crosslinked cellulose nano crystal (CNC) aerogels [109], Reprinted with permission

fat, etc., which function simultaneously with the connected body organs [114–116]. These tissues can be injured by disease, age, inherited defects, traumas resulting in malfunctions, disfigurement, or death. The structural properties and composition of scaffolds should match with the host natural ECM system to help cell growth and tissue regeneration in the applied area [117, 118]. Besides, scaffolds must be biocompatible with host tissue, transport nutrients within the cell matrix, porous enough to support cell accommodation.

In the past, several polymeric materials have been used to fabricate tissue scaffolds, which are distinguished into two broad classes: (i) natural and (ii) synthetic and their derivatives. Natural polymer includes proteins like collagen [119, 120], gelatin [121–123], elastin [124], prolamine [125], fibrinogen [126, 127] etc.) and polysaccharides which are cellulose [128, 129], alginate [130, 131], chitin [132], chitosan [17, 133], dextran [134] etc. are broadly used in soft tissue engineering. Alternatively synthetic polymer includes polyurethane (PU) [135, 136], poly(vinyl alcohol) (PVA) [137], polyacrylamide (PAM), polylactic acid (PLA) [5], polyglycolic acid (PGA), polycaprolactone (PCL) [138], polyhydroxyethyl methacrylate (pHEMA), poly(ethylene glycol) (PEG), polyethylene oxide (PEO), poly(acrylic acid) (PAA), and poly(propylene fumarateco-ethylene glycol) P(PF-co-EG) and their copolymers [139, 140]. Both the polymers are excellent candidates for the fabrication of tissue scaffolds due to their biodegradability, biocompatibility with low cytotoxicity, ability to transport nutrients and imitate host natural ECM.

The application of collagen-based scaffolds in soft tissue engineering has garnered much attention during the last decades. As a natural polymer, collagen possesses excellent properties to be successful as an excellent candidate for soft tissue engineering listed in Table 3. Collagen is the key part of ECM of soft, semi-rigid, and rigid connective tissues and responsible for ensuring not only the 3D structure but also for the growth of new tissues. Collagen, being an amphoteric macromolecule, the interaction between molecules, fibrils, and chain fragments due to intramolecular attraction, dipole–dipole, or hydrogen bonds, can form gels in the aqueous system at a pH outside of the isoelectric range. Besides the gels, collagen-based hydrogels exhibit superior structural and thermal properties, longevity, and biological properties due to the 3D polymeric networks established through cross-linking of gels. The three-dimensional structure guarantees the stability and physical integrity of the hydrogels. Natural bonding via cross-linking in vivo offers high structural integrity and strength and proteolysis resistance to collagen. Physical and chemical cross-linking are the two main types of in vitro methods to get collagen hydrogels. However, extensive cross-linking exhibits some drawbacks such as it can change the physical integrity of the hydrogels structure and cytotoxicity due to some chemical cross-linkers (e.g. glutaraldehyde). Grant et al. showed enhanced longevity of collagen constructs through decreasing the degradation rate of collagen while maintaining the microstructure [141]. They developed AuNPs induced collagen constructs and found that it exhibits only 7% degradation or loss of collagen compared to 100% degradation of pristine collagen via collagenase binding sites. They implanted the AuNP-collagen cohort into the subcutaneous space of swine ears and performed up to 6 months in vivo study. The implanted cohort exhibits superior biocompatibility and longevity compared to commercially available Hyaluronic acid (HA) induced collagen cohort. It can be attributed due to the conjugation of AuNPs to collagen fibrils allowing slow degradation through hindering collagenase binding sites.

Gelatin is another naturally derived polymer with low antigenicity compare to pristine collagen due to having degraded collagen. Gelatin can be used to construct various kinds of structures with superior stability and cell adhesion [148]. Gelatin-based scaffolds are promising candidates for tissue engineering due to the extensive viability, differentiation, and propagation of cells shown in Table 4. Kessler et al. developed methacrylated gelatin/hyaluronan scaffolds to investigate their interaction with human stem cells (hASCs) [8]. They photo-crosslinked methacrylated gelatin gels using crosslinker (lithium phenyl-2,4,6-trimethylbenzoylphosphinate) with hyaluronan to make the hydrogels. They used the hydrogel to examine the cell viability and adipose

Table 3 Summary of some recent reported collagen-based scaffolds

Materials	Fabrication techniques	Area of applications
Collagen/poly (3-hydroxybutyric acid)/gelatin [142]	Electrospinning	Skin tissue (wound healing)
Collagen/chitosan [143]	Freeze drying, dehydrothermal treatment	Skin tissue
Collagen hydrogel [144]	3D printing	Cartilage tissue
Collagen/elastin hybrid [145]	Excimer-laser ablation	Skin tissue
Collagen gel [146]	Molding technique	Vascular tissue
Collagen/alginate/fibrin [120]	Solution polymerization	Soft tissue
Collagen/silk fibroin [147]	Cross-linking	Corneal tissue

Table 4 Summary of some recent reported gelatin-based scaffolds

Materials	Fabrication techniques	Area of applications
Gelatin/PEG [150]	Cryogelation	Soft tissue (neural, cardiac and skin)
Gelatin/PU [123]	Electrospinning	Soft tissue
Dexamethasone (Dex)-loaded poly (glycerol sebacate) (PGS)-poly (caprolactone) (PCL)/gelatin (Gt) (PGS-PCL/Gt-Dex) [151]	Coaxial electro spinning	Soft tissue
Gelatin methacrylamide (GelMA)/poly(ethylene glycol) (PEG) [152]	Thiol-yne coupling	Soft tissue
Gelatin-chitosan [153]	Electrospray ionization	Injectable tissue engineering scaffolds
Gelatin/poly (glycerol-dodecanedioate) (PGD) [154]	Glectrospinning	Soft tissue
Gelatin/PCL [117]	Glectrospinning	Vascular tissue
Tecophilic/gelatin [118]	Glectrospinning	Blood vessel tissue

disintegration of ASCs for up to 30 days and observed satisfactory cell viability within 24 h. They found mature adipocytes due to adipogenic differentiation of ASCs and increased significantly until 28 days of culture. This can be due to the phenomenon that imitation of ECM composition and constant supply of foods to proliferated cells results in excellent cell viability, proliferation, and differentiation. Negrini et al. engineered gelatin-based hydrogels with varying structural properties using different concentrations and reaction parameters during the fabrication process [149]. To imitate the properties of adipose tissue (AT), the fabricated hydrogels should possess a wide range of properties to regenerate different AT depots. They developed four different (15GEL05, 15GEL1, 25GEL05, and 25GEL1) types of hydrogels using crosslinker like N–N′-methylene bis(acrylamide) (MBA) and different gelatin concentration (15 or 25% w/v_{water}) and/or their ratio during the fabrication process. The synthesized hydrogels showed elastic modulus ranging from 29 to 76 kPa, which is appropriate to imitate breast and heel pad AT. Among the above four hydrogels, 15 GEL05 showed superior results mimicking breast AT with no cytotoxic effects.

Elastin is the prime functional protein for most of the elastic tissue like skins, lungs, muscles, ligaments, tendons, blood vessels, etc., and plays a role in their physiological activities. Besides elastic properties, elastin needs to have structural stability, bioactivity, and biocompatibility for tissue engineering application. Pesqueira et al. (2018) introduced a unique approach to stimulate intrinsic healing tissue regeneration by using the strength of a magnetic field [155]. They developed magnetically responsive tropoelastin (soluble precursor of elastin) hydrogels induced with highly discrete nanoparticles in the matrix. The hydrogel showed high sensitivity (about 5 s) with the applied external magnetic field to trigger the healing capability without changing the elasticity of the materials. The fabricated hydrogel exhibits high cell cultural increased ($p < 0.0001$) activity compared to the control system (tropoelastin alone) after 14 days of incubation. This study widens the application area of elastin protein including, wound healing, cell growth in the injured area.

Plant proteins also offer some excellent properties which make them promising candidates for soft tissue scaffolds precursors such as readily available, biodegradable, non-toxic, amphiphilic nature, antimicrobial effect, high morphological and structural properties etc. Vogt et al. used zein, plant protein with poly (glycerol sebacate) (PGS) to fabricate soft tissue scaffolds for cardiovascular tissue regeneration or reconstruction [125]. They electrospun zein-PGS fiber mats to imitate ECM structure to overcome the drawbacks of donor site morbidity, foreign body response, malformation, complications etc. They found that the zein-PGS fiber showed limiting mechanical improvement in aqueous solvent whereas fiber induced with N-(3-Dimethylaminopropyl)-N′-ethylcarbodiimide(EDC)/N Hydroxysuccinimide (NHS) exhibits enhanced mechanical and morphological properties.

Alginate polysaccharide is another abundant natural polymer widely used for cell encapsulation as well as in vivo cell, drugs, protein delivery. Researchers have done tremendous studies on alginate embedded hydrogels for cell regeneration. But most of the alginate hydrogels possess degradation problems as in vivo application. To tackle this limitation, researchers tried to develop alginate hydrogels induced with cross-linking agents to enhance mechanical integrity and stability. Deepthi et al. developed alginate nanobeads fibrin hydrogel through calcium cross-linking with high material integrity and showed mechanical strength of 19 kPa [130]. This injectable hydrogel offers high material integrity, high surface area, improved growth factor and cell delivery. The excellent biocompatibility behavior of alginate gel was investigated via hMSC viability and adhesion test. They observed outstanding cell retention behavior of the developed hydrogel as well as cell growth and proliferation. As it is the prerequisite of soft-tissue scaffolds to possess mechanical integrity and compatibility with the application field, alginate-based hydrogel mimics the elasticity and strength of the soft tissue that made them an excellent candidate for soft tissue regeneration and reconstruction. Markstedt et al.

developed human chondrocytes scaffold via a 3D bioprinting technique using alginate and nanofibrillated cellulose (NFC) hybrid hydrogel for soft tissue application [156]. The fast cross-linking behavior of alginate and shear thinning properties of NFC made possible this 3D bio-ink printing. The cytotoxic and cell feasibility test ensures the 3D printed scaffold is an outstanding candidate for the growth of cartilage tissue. They observed promising cell viability of the scaffolds of 73% and 86% after 1 and 7 days of culture. This is due to the excellent biocompatibility and potential media for cell culture of the alginate/nanocellulose hydrogel.

Carboxymethyl cellulose (CMC), another form of regenerated cellulose, is an excellent candidate for biomaterials application due to its outstanding chemical properties listed in Table 5. But CMC showed some difficulties via polyelectrolyte complex formation during nanofiber formation, which limits its application. To overcome this drawback, Basu et al. fabricated CMC/PEO (polyethylene oxide) nanofibrous scaffolds through electrospinning technique for soft tissue engineering applications [3]. The higher charge density of CMC/PEO solution favors forming nanofibrous scaffolds via electrospinning technique. The fabricated scaffold showed promising cell proliferation, non-toxic, and metabolic activity, which implies their potential applications in tissue engineering.

Chitosan, a deacetylated derivative of chitin, is one of the most prominent biomass polysaccharides, possesses excellent biocompatibility, biodegradability, nontoxicity, and adsorption properties. Though chitosan-based scaffolds have so many promising properties for numerous applications, including biomedical, tissue engineering, drug delivery etc., listed in Table 6 but low mechanical strength restricts its wide applications. Researchers tried to enhance the structural strength of chitosan-based scaffolds (Fig. 7) by blending them with other synthetic or natural polymers reported in the literature [119, 163]. Polyurethane is one of the most extensively used synthetic polymers in the biomedical field due to its outstanding biocompatibility with high physical and mechanical properties. Oliveira et al. fabricated a chitosan-based bilayered scaffold with hydroxyapatite (HA/CS), having optimized structural integrity and strength for osteochondral application [164]. The fabricated scaffold exhibited outstanding cell viability, propagation, and differentiation of osteoblasts and chondrocytes, respectively. These results widen the application area of chitosan in the field of biomedical and tissue engineering applications.

Wound Healing

The vertebrate body's largest organ is the skin, which provides the principle exterior defense system against external attacks such as contamination, infection, and the effect of harsh external environments. Besides protecting its role in sensory detection, regulating body temperature, fluid homeostasis, and self-healing is also crucial. Skin is usually composed of three parts such as thin and high cellular epidermis, acts as a barrier of the body that protects the body from external injuries and controls the loss of fluid during

Table 5 Summary of some recent reported alginate-based scaffolds

Materials	Fabrication techniques	Area of applications
Alginate/collagen (Type I/Type II) [157]	Freeze drying	Cartilage tissue
Alginate and gelatin [158]	Cross-linking	Soft tissue
Alginate/O-carboxymethyl chitosan/nano fibrin [159]	Ionic cross-linking	Adipose tissue
Alginate nanobeads/fibrin [130]	Double syringe apparatus (duplojet applicator)	Soft tissue
Alginate foam [160]	Freeze drying	Soft tissue
Polypyrrole/Alginate [161]	Ionic cross-linking	Neural Tissue
Alginate/gelatin [162]	Cross-linking	Wound Healing

Table 6 Summary of some recent reported chitosan-based scaffolds

Materials	Fabrication techniques	Area of applications
Chitosan/keratin/gelatin [16]	Freeze-drying	Soft tissue
Chitosan/hyaluronan [165]	Metal-free click chemistry	Soft tissue
Chitosan-poly(Ɛ-caprolactone) dialdehyde [133]	Cross-linking	Soft tissue
Agarose-chitosan coated silver nanoparticle [17]	Cross-linking	Soft tissue
chitosan/PVA/methylcellulose [166]	Freeze-drying	Soft tissue
Chitosan nanofibrous mats [167]	Electrospinning	Soft tissue regeneration
Chitosan/methacrylated silk fibroin [168]	Photopolymerization	Cartilage tissue

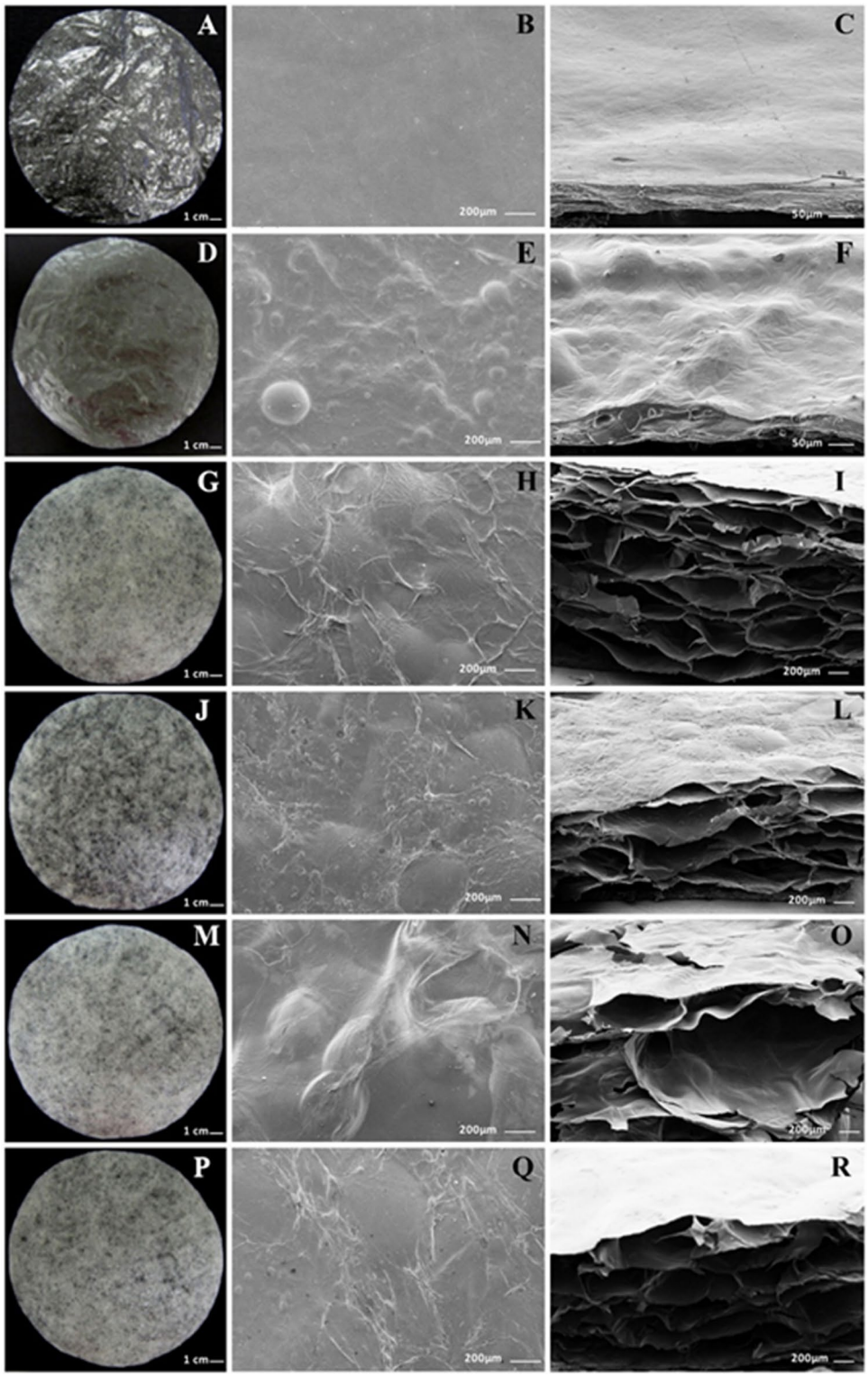


Fig. 7 Chitosan-based scaffolds for soft tissue engineering; first column-classical view, middle column-surface morphology and third column-cross-sectional view of chitosan-xanthan gum, Ch-X (**A**–**C**), Ch-X porous scaffolds, Ch-X-S (**D**–**F**), Ch-X with surfactant Kolliphor (10% w/w), Ch-X-K10 (**G**–**I**), Ch-X-S-K10 (**M**–**O**), and Ch-X-S-K25 (**P**–**R**) formulations. Reprinted with permission [119]

the injuries [169], the acellular dermis, usually consists of the collagen-rich extracellular matrix, providing the physical strength and flexibilities to the skin it accommodates the nerve bundles, vasculature, and lymphatic system [170, 171] and the inner layer of subcutaneous fat tissue is known as hypodermis that provides the thermal isolation and mechanical protection from outer injuries [169], as seen in Fig. 8.

The skin has three layers of protection, yet it gets damaged due to different reasons such as injuries, reduced blood circulations, burns, and aging. These damages or injuries

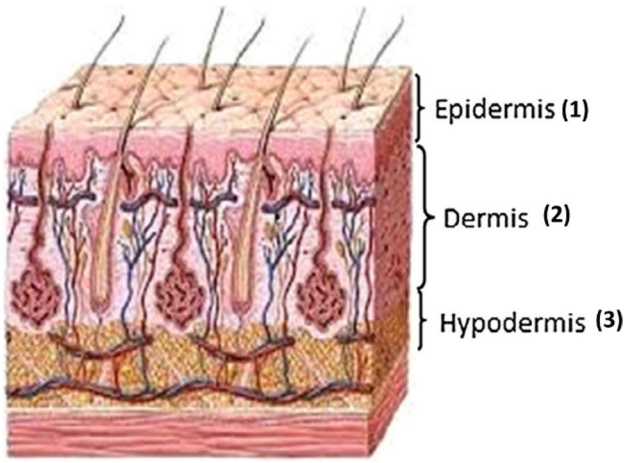


Fig. 8 Schematic representation of normal skin structure [169], which has three layers: epidermis, dermis, and hypodermis

which disrupt the regular function and anatomic structure of skin are collectively defined as the wound [172]. Minor wounds can heal by themselves without additional treatment, whereas severe wounds require additional treatments to heal. Without proper treatment, during the major wounds, the skin's integrity can be severely compromised and lead to deleterious outcomes such as morbidity and mortality [173].

Classification of Wounds

Healing time plays a crucial role in wound repair and injury management, and based on healing time, wounds can be classified into two major categories: (1) acute wounds and (2) chronic wounds [174]. The subcutaneous layers get compromised during the acute injuries due to the damage in the epidermis or superficial dermis region [175]. The main contributing factors for acute wounds are surgical incisions, thermal injuries, abrasions, and lacerations. In comparison, choric wounds are caused by specific diseases such as diabetes, tumors, and severe physical conditions [176], and chronic wounds reappear frequently [177]. Choric wounds usually take more than 12 weeks to heal [178], whereas acute wounds get cured within 8–12 weeks [179]. Apart from the healing process and time, wounds can be classified in four other ways based on appearances of injuries [177]. Another criterion for the wound classification is the number of affected layers and areas of wounded skin. Based on this criterion, it can be classified into three major types [172]. The overall classification of wounds is depicted in Fig. 9.

Concept of Wound Healing

Correct and efficient wound healing is essential for the continuation of life. From the ancient time-efficient healing was a daunting task, which still poses a challenge for the physicians and scientists. The animal body consists of different tissues and organs, and any part of the body can experience wounds. Even though different body parts have different cell structures, most of the wounded cells or body parts heal following a similar pattern. From inception to heal, wound healing is a continuous process. However, for understanding purposes, the overall healing process was divided into several phases. Synchronized interactions between the different immunological and biological systems are a prerequisite for the successful recovery of a wound. Healing has a precise consecutive regulated step that correlates various cell types in the wound bed during the individual stages of healing. These steps are summarized into four consecutive events: (1) coagulation and hemostasis, starts right after any incident; (2) inflammation, right after earlier event, (3) proliferation, which begins within few days of the injury and

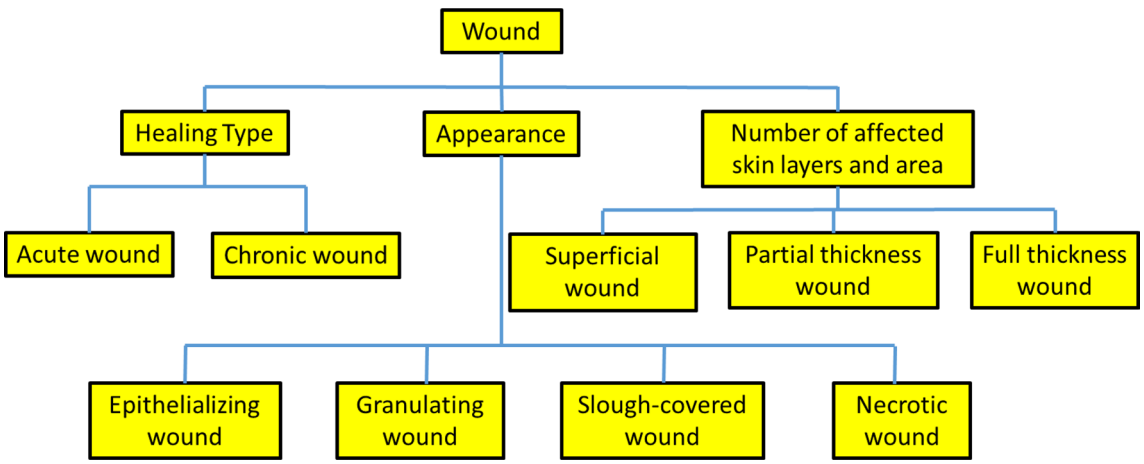


Fig. 9 Wounds are categorized into three significant aspects, and those individual aspects have several other types of wounds

comprehends the main healing progressions, and (4) wound remodeling, where the formation of scar tissue takes place. The last phase, wound remodeling, can last up to a year or more. Wound healing steps are schematically represented in Fig. 10. The coagulation and hemostasis primarily prevent the exsanguination. While preventing exsanguination, it protects the vascular system by keeping it intact, so vital organs' function remains undamaged despite injury [174]. The inflammatory phase follows the hemostasis and takes approximately 24 h to form the injury to begin. Against invading micro-organisms, inflammation establishes a resistant barrier. Two separate phases constitute the entire inflammation stage: the early inflammatory phase and the late inflammatory phase [174]. The proliferation began roughly on the third day of wounding and continued for the next 2 weeks. During this phase, the wound gets covered by epithelium, and new granulating tissues are formed. Microphages, fibroblasts, and blood vessels come simultaneously near the wound bed and act as a single unit during this phase [177]. The remodeling phase is responsible for new epithelium and final scar tissue formation. Scar tissue formation can take 1–2 years or longer [174, 180]. In-depth healing mechanisms are beyond is the article's scope, and interested readers can go through the following literature [174, 181, 182] to know the wound healing mechanism in detail.

Required Properties for Ideal Dressing Materials

Wound healing treatment has been evolved significantly over time. However, the requirements for ideal healing remained similar. Selecting the appropriate dressing system based on the type of wound is the main requirement for good healing. Since its inception, different healing materials were used, which are broadly classified based on different criteria. Based on the source, frequently used wound dressing materials are categorized into three types [183]: (1) biologic, (2) synthetic, (3) biologic-synthetic composite. Every kind of dressing material has unique properties, which is why these sealants are applied to specific kinds of wounds. Irrespective application and categories, all the dressing materials should possess the some properties such as keep a suitable moist environment with exudates around the wound bed, allow gaseous exchange, remove excess exudates while acting as a barrier to microorganisms, free of infection, non-toxic, non-allergenic, non-sensitizing, fully biocompatible, easily removable from the wound site without any trauma, readily available with minimal processing time and cost, antimicrobial properties, thermal insulation, promotes wound healing and stimulate the growth factor [169, 177, 183] to be considered as good dressing material.

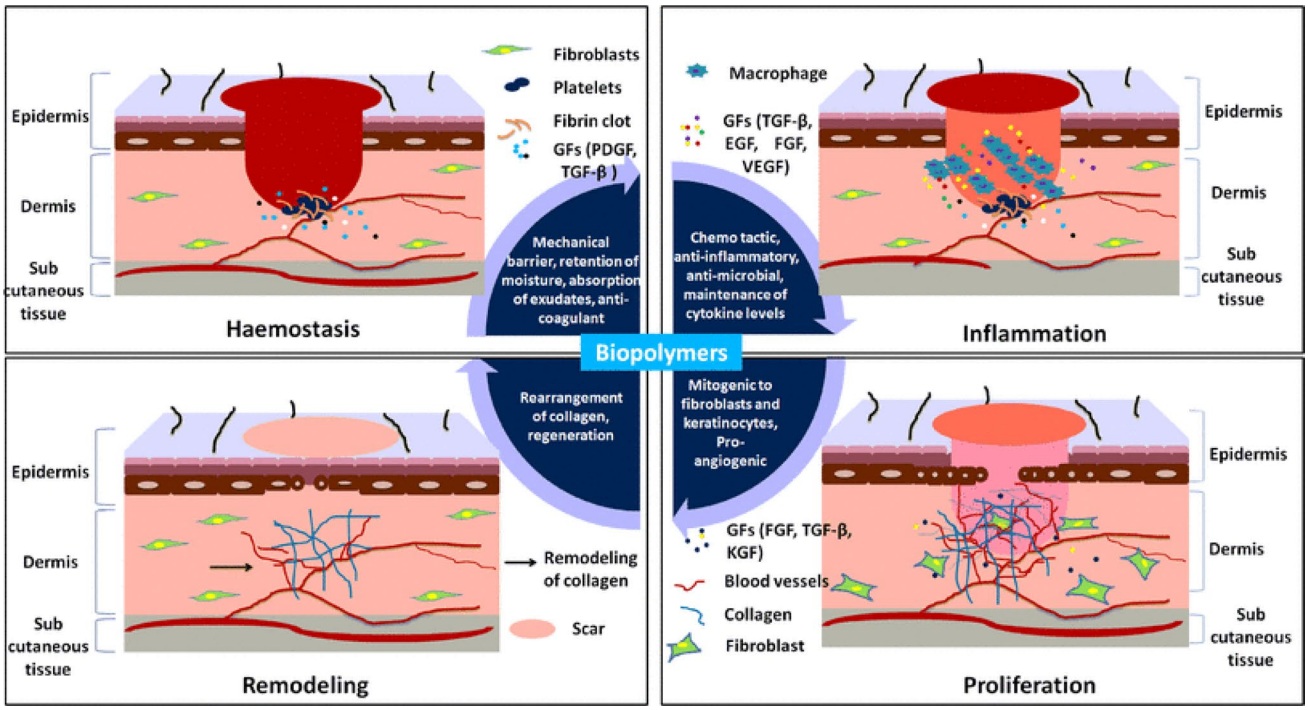


Fig. 10 Schematics of wound healing phases [186]. Hemostasis begins right after the injury, which is followed by the inflammation stage. Proliferation is the third phase of healing the injury and one of the key phases of wound healing. Finally, scar tissue formation takes place in the remodeling phase

Biopolymers in Wound Healing

Biopolymers or natural polymers are the principal candidates for wound and burn healing. Natural polymers have extensive use in dressing a wound or burn injury due to their biocompatibility, biodegradability, and resemblance to ECM [184, 185]. The main sources of these organic healing materials are living organisms such as fungi (chitin), algae (alginate), bacteria (bacterial cellulose, exopolysaccharides), plant (starch, cellulose, and natural rubber), and animal (collagen, hyaluronic acid, chitosan) [186]. A sequence of repeating units held by different covalent bonds form these biopolymers, such as monomers of amino acids, nucleotides, monosaccharides, etc. held by covalent bonds form the biopolymer peptides, polyphenols, polysaccharides, or polyesters, etc. Because of the 3D network structure, these biopolymers can easily be saturated with water or biological fluids. These ingrained healing characteristics made them the active choice for pharmaceutical and biomedical applications, exclusively for wound healing, tissue engineering, drug delivery, and implants [187].

Collagen is one of the essential structural proteins of any organ and is mostly found in connective tissues. ECM and collagen have similar structural and functional characteristics, which further inspired the use of collagen matrices in wound healing applications. Chemically collagen has a triple helix fibril structure where a repeating amino acid polymer is held by peptide linkages. Collagen plays a pivotal role in natural healing, from the clotting induction to the development and appearance of the final scar. Fibroblast's formation in damaged tissues is stimulated, and the migration of endothelial cells is accelerated once the damaged tissue gets in contact with collage. Knapp et al. [188] first reported the medical usage of external collagen in human. They prepared allogenic and xenogeneic source-based collagen, which further used a structural basis for soft tissues. Since then, twenty-nine types of collages were identified, and among those, I, II, and III types have extensive use in wound healing [186]. Bovine, porcine, and avian are the primary sources for natural or bio collagen dressing formulation [189]. Different forms of collagen have numerous biomedical applications in literature, and a few of the applications are tabulated in Table 7.

Chitin is the second most used biopolymers in wound healing [196]. Chitins are inert polysaccharide copolymer and extracted from the invertebrates (crustacean shells or insect cuticles, mushroom envelopes, green algae cell walls, and yeasts). Chitosan is derived from chitin, which is the active and partial deacetylated form of chitin. Their biocompatibility, biodegradability, non-toxicity, antimicrobial, and hydrating properties made them ideal candidates for wound healing, especially for open and deep wound healing. These have the haemostatic effect that accelerates fibroblasts layer formation during the healing [168]. Chitin and chitosan were used with other polymers to make hydrogels, foams, scaffolds, etc. and these copolymers have extensive use in wound dressing applications (Table 8). The chitin and chitosan derived polymers are extensively used in wound healing; however, they are still expensive due to their handing issues [168].

Cellulose is a plant-derived polymer and extensively used in wound healing. The repeating units of β-d-glucose connected by β-1, 4-glycosidic linkages formed the cellulose structure. Film obtained from the cellulose exhibits outstanding properties such as high purity, good tensile strength, high exudates capacity, biodegradability, and unique nanofibril morphology network structure [168]. Cellulose usually keeps wound moist and moist wounds heal more rapidly due to enough supply of growth factors and other nutrients to the healing tissues [185]. Along with these outstanding properties, cellulose-based films have some drawbacks, such as a lack of antibacterial

Table 7 Applications of collagen in wound healing

Application	Material	Formation	References
Wound dressing	Thermostable and biodegradable fibril	Collagen–alginic acid cross-linking	[190]
Skin diseases, anti-oxidant, severe burns	Collagen-α-tocopherulate biopolymer	Solid-phase synthesis	[191]
Artificial vascular grafts and wound repair	Nanofibrous collagen scaffolds	Electrospinning	[192]
Skin grafting	Microfiber scaffold	Collagen seeded with human fibroblasts and keratinocytes	[193]
Cutaneous wound infections	Hydrogels	Type I collagen and minocycline hydrogel were prepared by response surface methodology and Taguchi's approach	[194]
Gingival wounds	Collagen-glycosaminoglycan complex	Type 1 collagen (80%) extracted and purified from calfskin, nasal septa of newborn lambs were used for chondroitin 4-sulfate (13%), and heparan sulphate (6.5%) were extracted from ovine placenta	[195]
Deep skin wounds	Sponges	Chemically reaction of hexamethyldiisocyanat with collagen	[196]

Table 8 Chitin and chitosan-based biomaterials for various types of wound healing

Application	Material	Formation	References
Burn and postoperative or posttraumatic wounds	Dibutyrylchitin	Under the heterogeneous condition, the reaction between shrimp chitin and butyric anhydride creates di-butyryl chitin, perchloric acid act as a catalyst during the formation	[197]
Cutaneous wounds in diabetic models wound contraction	Chitin-based hydrogels	Chitin hydrogel was developed with appropriate deacetylation degree and molecular weight	[198, 199]
Soak up wound exudates, helping the tissue regeneration, filling material	Sponges	Freeze-drying (lyophilization): freezing of chitosan solution followed by solvent sublimation under reduced pressure	[200]
Skin repair, haemostatic dressing	2D-scaffolds and films	Wet casting of chitosan salt solutions, dry the cast in an oven or use infrared (IR) for drying	[186, 201]
Wound dressing	Nanofiber membranes	Dry and wet spinning, electrospinning	[202, 203]

protection in the wounded areas, restricting its extensive use as dressing materials [168]. Alginic acid is usually extracted from the brown algae and it comprises a linear copolymer of α-L-guluronic acid and β-D-mannuronic acid. Alginate absorbs the exudates while keeping the wound bed moist. They also reduce the pain, lower the infection, reduce the odor of the wound, most importantly, helps in hemostasis [204]. Initially, it was applied as a gel, whereas its recent uses were mostly seen as sponges. Hyaluronic acid protects an injured area from microorganisms by using its bacteriostatic property. The anti-inflammatory and pro-inflammatory properties are the characteristic features of high molecular weight and low molecular weight hyaluronan, respectively [185]. It helps in the remodeling of ECM and keratinocyte migration, it also plays a pivotal role in stimulating fibroblast proliferation. Gelatin is a collagen-derived protein. In skin tissue engineering, gelatin showed extensive epithelialization and granulation tissue formation [170]. Wound dressing hydrogel membranes were prepared by blending PVA with gelatin and those membranes showed a good result on fibroblast culture and proliferation. In addition to these reported biopolymers, some other natural polymers such as starch, fucoidan, glucan, dextran, keratin, and silk, etc., have shown decent assistance in wound healing. Exploring the full potential and capabilities of these materials in facilitating wound healing requires more detailed studies.

Miscellaneous Applications

Miscellaneous applications include various potential application areas of both natural and synthetic biopolymers such as biosensors, medical and hygiene fields. This section discusses these promising application areas of biopolymers.

Biosensor

Recent advancement of technology helps to explore the development of new electrochemical biosensor architectures broadly for healthcare monitoring [205]. Some of the most extensively studied polysaccharides in this field are chitosan and carboxymethyl cellulose [206, 207], due to their extraordinary properties include biodegradability, biocompatibility, non-toxicity, adherent thin films forming ability, renewable, and abundant in nature [208, 209]. Another kind of biopolymer, laccases at the enzyme's active center contain copper atoms' cluster known as glycoproteins, which transfer electrons during redox reactions, including the reduction of molecular oxygen to water and the oxidation in the reduced form of phenolic compounds [210]. Biosensors based on laccase permit phenolic compounds to be directly investigated in complex matrices because of their sensitivity and selectivity. They are also beneficial due to rapid responses and miniaturization possibility, simplicity of fabrication, low cost, potential ability for on-site and real-time analysis. Biosensors developed from laccase can be used in the indirect determination of drugs that refer to parallel reactions, which can occur in enzymatic reactions with substrate or product. Sartori et al. developed a voltametric sensor using polyphenol oxidase, an extract of sweet potato to investigate the presence of a sulfite in wine samples (*Ipomoea batatas* (L.) Lam.) [211]. Here sulfite acts as a nucleophile that reacts with o-quinone to form o-quinone sulfite. Biosensors can be used as suitable alternative strategies to develop precise, simple, and effective analytical methods for indirect determination of spironolactone in the treatment of critical hypertension, liver cirrhosis, and congestive heart failure [212].

Carbonaceous nanomaterials, such as multi-walled carbon nanotubes (MWCNTs), have been broadly used to modify surfaces of electrodes to develop new architectures of biosensors [208, 213]. These sensors exhibit a high potential to

transport electric signals that are generated upon biological response recognition, which result from a biochemical reaction between the target analyte and the enzyme immobilized on the sensor surface. The small size MWCNTs enhances the electrochemical efficiency of bulk electrodes via promoting a high transmission electronic signal between the electrode/solution interfaces, thereby increasing the sensitivity and lowering the detection limits.

Medical and Hygiene

Biopolymers have significant usage for various medical applications for occlusion, suturing, covering, fixation, isolation, adhesion, cellular proliferation, controlled drug delivery, contact inhibition, tissue guide, etc (Table 9). Poly-(L-lactic acid), poly-(glyconic acid) and copolymers of them are widely used as sutures because they offer exceptional flexibility and reliant knot robustness [214, 215]. Poly(ortho ester) and poly-hydroxy groups are mostly used for drug delivery. Polyurethanes have flexible, robust, wear, and tear properties that are significant for grafting scaffold facilitating artificial blood vessels [216]. Polyesteramides which have good mechanical and thermal properties, are used to facilitate drug delivery, hydrogel, and tissue engineering application. Hospitals are primarily used hygiene and healthcare products such as surgical masks, gloves, surgical gowns, towels, sanitary napkins, diapers, bedding, surgical footwear and headwear, panties shields, antimicrobial textiles, surgical drapes, wipes, etc. which are both disposable and non-disposable. Biobased PET can be used for surgical gowns instead of conventional cotton, polyester, and polyethylene [217]. Polylactic acid is used for the purpose of

Table 9 Applications of biopolymers in the medical field [214–219]

S.no	Abbreviation	Full name	Properties suitable for medical applications	Application
1	PLA	Polylactic acid	-PLA degrades within the body after the incision has healed -Copolymers of PLA and PGA are more useful than homopolymers of PLA and PGA because their rate of degradation can be adjusted	-Devices made of PLA-PGA copolymers have been used for the controlled release of antibiotics, anticancer and antimalarial agents, contraceptives, hormones, insulin, narcotic antagonists, and proteins -Suture
2	PGA	Polyglycolic acid	-Insoluble in water -Biodegradable	-Drug delivery -Tissue engineering
3	PLGA	Poly(lactic-co-glycolic acid)	-Tailored biodegradation rate (depending on the molecular weight and copolymer ratio) -Potential to modify surface properties to provide better interaction with biological materials -Degrades rapidly than PGA and PLA -Amorphous (prop. Depend on MW crystallinity	-Ligament/Tendon Repair -Biodegradable Stents -Bone fixation devices
4	PCL	Polycaprolactones	•Biodegradable •Good water, oil, solvent and chlorine resistance	•Drug-delivery systems •Sutures •Wound dressing •Contraceptive devices •Fixation devices •Dentistry •Tissue engineering
5	PEA	Polyesteramides	•Good thermal and mechanical properties •Hydrophilic/hydrophobic ratio and biodegradability can easily be tuned	•Drug delivery •Hydrogels •Tissue engineering •Smart materials (T sensitive) •Hot-melt adhesive
6	PBAT	Polybutyrate adipate terephthalate	•Flexible, high elongation at break •Poor mechanical and thermal resistance •Random copolymer	•Packaging applications •Bottle applications (blend with PLA
7	PHB	Polyhydroxybutyrate	•Optical activity, piezoelectricity •Excellent barrier and mechanical Properties •Biodegradable	•Surgical implantPackaging •Microcapsules
8	TPS	Thermoplastic Starch	•Biodegradable •A favorable set of mechanical properties •Products made of it have good dimensional stability in application conditions	•Packaging

Table 10 Possible biopolymer applications in the medical field [220]

S.no	Application	Polymer used	Possible biopolymer replacement
1	Suture	Poly(amide), poly(propylene), Poly (vinyliden fluoride)	PLA, PGA, PLGA
2	Wound dressing	Poly (vinyl alcohol), cotton	PGA, PLA
3	Tubing or blood bags	Poly (vinyl chloride)	PBAT, PHB
4	Catheters	High-density polyethylene (PE), Poly (dimethylsiloxane), polyether ether ketone, poly (propylene)	PLA, PGA, PLGA, TPS, PCL
5	Plasters	Toluene 3, 4 diisocyanate and polyethylene glycols (Lycra fibers)	PLA, TPS
6	Surgical gowns	Cotton, polyesters, polypropylene (PP), PE	Biobased (PET, PBT)
7	Caps, masks, and gowns	Polyethylene terephthalate, cotton	PLA, TPS
8	Surgical hosiery	PET, cotton, PP, PE	Biobased PET
9	Pillow cover	Polyesters	PLA, TPS
10	Uniforms	Polyesters	Biobased PET, TPS, PLA
11	Baby diapers	Polyacrylic acid, polyvinyl alcohol copolymers	TPS

making gowns, masks, and caps [218]. Thermoplastic starch is used for making baby diapers because of its super absorbent property [219]. Biomaterials, including alginate fibers, catgut, collagen, chitosan, and super absorbent polymer, are also used mainly for medical and hygiene applications. Table 10 presents the possible applications of biopolymers in the medical and hygiene fields.

Summary and Future Perspectives

In this review, we presented the potential use of biopolymeric materials in the field of biomedical applications, which have found to be increased significantly to a great extent unambiguously by considering their characteristic properties, including mechanical, thermal, compatibility, optical, and so on, the most promising state-of-the-art processing methods for the fabrication of smart biopolymers along with an overview of the diverse applications in the biomedical fields. The various synthetic routes developed for preparing biopolymers during research findings are compiled, along with their significant parameters for multiple applications. Based on the research findings, it could be suggested that the development and improvement of various biopolymeric materials through functionalization or hybridization with different functionalities are very important for target-oriented biomedical applications. For example, the blending of biopolymers with other biodegradable polymers could be one of the best ways to prepare new polymeric systems with "tailor-made" functional properties such as physical properties and biodegradability. The preparation of bio nanocomposites is a promising method to enhance the polymeric properties while the final polymer can maintain biodegradability. Despite the much improvement made in the field of biomedicals by using biopolymers, significant studies should be carried out for making suitable drug delivery systems, which could be a more robust method with reliability. In addition, the knowledge of the mechanism and time taken for the drug delivery system for a tissue or cellular compartment in respect to objective is critical. These are the challenges to address the unresolved medical need over time.

Future advances in implementing various biopolymeric systems in therapeutics applications, including the capability to scale up with controlled and targeted properties, could be a significant step for the future as the proper nanocarrier is essential to carry the DNA or genetic material to the targeted site. Therefore, efficient processing methods for harvesting such biopolymeric systems need to be prioritized as they will be used more in biological systems. It could also be strongly suggested that computational models can be integrated to interpret the effects on the profile of the materials, such as degradation profile and intra- and extra-cellular trafficking of polymeric nanoparticles for increased commercialization. Therefore, intense research on the surface and functionalization of biopolymers such as nanocellulose is potentially required to bring a revolutionary breakthrough of biomedical materials because modification of either chemical or surface could significantly alter the cell-material interaction properties. This review has provided promising results from recent studies, which will open a new avenue for developing more advanced smart biopolymers with controlled functional properties, guiding a platform for designing more efficient biopolymers for biomedical applications.

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Declarations

Conflict of interest The authors declare no conflicts of interest.

References

1. Babu RP, O'Connor K, Seeram R (2013) Current progress on bio-based polymers and their future trends. Prog Biomater 2(1):1–16
2. Rangari VK, Biswas MC, Tiimob BJ (2019) Biodegradable polymer blends for food packaging applications. In: Cruz RMS (ed) Food packaging innovations and shelf-life. CRC Press, Boca Raton, p 151
3. Basu P, Repanas A, Chatterjee A, Glasmacher B, NarendraKumar U, Manjubala I (2017) PEO–CMC blend nanofibers fabrication by electrospinning for soft tissue engineering applications. Mater Lett 195:10–13
4. Ren CD, Kurisawa M, Chung JE, Ying JY (2015) Liposomal delivery of horseradish peroxidase for thermally triggered injectable hyaluronic acid–tyramine hydrogel scaffolds. J Mater Chem B 3(23):4663–4670
5. Hoque ME, Ghorban Daei JM, Khalid M (2018) Next generation biomimetic bone tissue engineering matrix from poly (L-lactic acid) PLA/calcium carbonate composites doped with silver nanoparticles. Curr Anal Chem 14(3):268–277
6. Bacakova L, Pajorova J, Bacakova M, Skogberg A, Kallio P, Kolarova K, Svorcik V (2019) Versatile application of nanocellulose: From industry to skin tissue engineering and wound healing. Nanomaterials 9(2):164
7. Song R, Murphy M, Li C, Ting K, Soo C, Zheng Z (2018) Current development of biodegradable polymeric materials for biomedical applications. Drug Des Dev Ther 12:3117
8. Kessler L, Gehrke S, Winnefeld M, Huber B, Hoch E, Walter T, Wyrwa R, Schnabelrauch M, Schmidt M, Kückelhaus M (2017) Methacrylated gelatin/hyaluronan-based hydrogels for soft tissue engineering. J Tissue Eng 8:2041731417744157
9. Nitta SK, Numata K (2013) Biopolymer-based nanoparticles for drug/gene delivery and tissue engineering. Int J Mol Sci 14(1):1629–1654
10. Balmayor ER, Tuzlakoglu K, Marques AP, Azevedo HS, Reis RL (2008) A novel enzymatically-mediated drug delivery carrier for bone tissue engineering applications: combining biodegradable starch-based microparticles and differentiation agents. J Mater Sci Mater Med 19(4):1617–1623
11. Gunatillake PA, Adhikari R (2003) Biodegradable synthetic polymers for tissue engineering. Eur Cell Mater 5(1):1–16
12. Chung HJ, Park TG (2007) Surface engineered and drug releasing pre-fabricated scaffolds for tissue engineering. Adv Drug Deliv Rev 59(4–5):249–262
13. Dhandayuthapani B, Yoshida Y, Maekawa T, Kumar DS (2011) Polymeric scaffolds in tissue engineering application: a review. Int J Polym Sci 2011:1–19
14. Kenar H, Ozdogan CY, Dumlu C, Doger E, Kose GT, Hasirci V (2019) Microfibrous scaffolds from poly (l-lactide-co-ε-caprolactone) blended with xeno-free collagen/hyaluronic acid for improvement of vascularization in tissue engineering applications. Mater Sci Eng C 97:31–44
15. Velema J, Kaplan D (2006) Biopolymer-based biomaterials as scaffolds for tissue engineering. Adv Biochem Eng Biotechnol I:187–238
16. Kakkar P, Verma S, Manjubala I, Madhan B (2014) Development of keratin–chitosan–gelatin composite scaffold for soft tissue engineering. Mater Sci Eng C 45:343–347
17. Kumar N, Desagani D, Chandran G, Ghosh NN, Karthikeyan G, Waigaonkar S, Ganguly A (2018) Biocompatible agarose-chitosan coated silver nanoparticle composite for soft tissue engineering applications. Artif Cells Nanomed Biotechnol 46(3):637–649
18. Gopi S, Amalraj A, Thomas S (2016) Effective drug delivery system of biopolymers based on nanomaterials and hydrogels-a review. Drug Des 5(129):2169–0138
19. Davidenko N, Cameron R, Best S (2019) Natural biopolymers for biomedical applications. Elsevier, Amsterdam, pp 162–176
20. Pattanashetti NA, Heggannavar GB, Kariduraganavar MY (2017) Smart biopolymers and their biomedical applications. Procedia Manuf 12:263–279
21. Rebelo R, Fernandes M, Fangueiro R (2017) Biopolymers in medical implants: a brief review. Procedia Eng 200:236–243
22. Sadegh-Zadeh K (2007) The fuzzy polynucleotide space revisited. Artif Intel Med 41(1):69–80
23. Riedel U, Nickel J (1999) Natural fibre-reinforced biopolymers as construction materials–new discoveries. Die Angew Makromol Chem 272(1):34–40
24. Oh JK, Lee DI, Park JM (2009) Biopolymer-based microgels/nanogels for drug delivery applications. Prog Polym Sci 34(12):1261–1282
25. Singh AV (2011) Biopolymers in drug delivery: a review. Pharmacologyonline 1:666–674
26. Gombotz WR, Pettit DK (1995) Biodegradable polymers for protein and peptide drug delivery. Bioconjugate Chem 6(4):332–351
27. Luo Y, Wang Q (2014) Zein-based micro-and nano-particles for drug and nutrient delivery: a review. J Appl Polym Sci 131(16):40696
28. Bajpai A, Choubey J (2005) Release study of sulphamethoxazole controlled by swelling of gelatin nanoparticles and drug-biopolymer interaction. J Macromol Sci 42(3):253–275
29. Liu L, Fishman ML, Hicks KB (2007) Pectin in controlled drug delivery–a review. Cellulose 14(1):15–24
30. Li Y, Hu M, Xiao H, Du Y, Decker EA, McClements DJ (2010) Controlling the functional performance of emulsion-based delivery systems using multi-component biopolymer coatings. Eur J Pharm Biopharm 76(1):38–47
31. Jacob J, Haponiuk JT, Thomas S, Gopi S (2018) Biopolymer based nanomaterials in drug delivery systems: a review. Mater Today Chem 9:43–55
32. Bhola R, Bhola SM, Liang H, Mishra B (2010) Biocompatible denture polymers-a review. Trends Biomater Artif Organs 23(3):129–136
33. Shelke NB, James R, Laurencin CT, Kumbar SG (2014) Polysaccharide biomaterials for drug delivery and regenerative engineering. Polym Adv Technol 25(5):448–460
34. Luo Y, Wang Q (2014) Recent development of chitosan-based polyelectrolyte complexes with natural polysaccharides for drug delivery. Int J Biol Macromol 64:353–367
35. Sultana F, Manirujjaman M, Imran-Ul-Haque MA, Sharmin S (2013) An overview of nanogel drug delivery system. J Appl Pharm Sci 3(8):95–105
36. Maiti S, Ranjit S, Sa B (2010) Polysaccharide-based graft copolymers in controlled drug delivery. Int J PharmTech Res 2(2):1350–1358
37. Liu Z, Jiao Y, Wang Y, Zhou C, Zhang Z (2008) Polysaccharides-based nanoparticles as drug delivery systems. Adv Drug Deliv Rev 60(15):1650–1662
38. Janes K, Calvo P, Alonso M (2001) Polysaccharide colloidal particles as delivery systems for macromolecules. Adv Drug Deliv Rev 47(1):83–97
39. Cui W, Li J, Decher G (2016) Self-assembled smart nanocarriers for targeted drug delivery. Adv Mater 28(6):1302–1311

40. Debele TA, Mekuria SL, Tsai HC (2016) Polysaccharide based nanogels in the drug delivery system: application as the carrier of pharmaceutical agents. Mater Sci Eng C 68:964–981
41. Bernkop-Schnürch A, Dünnhaupt S (2012) Chitosan-based drug delivery systems. Eur J Pharm Biopharm 81(3):463–469
42. Yang Y, Wang S, Wang Y, Wang X, Wang Q, Chen M (2014) Advances in self-assembled chitosan nanomaterials for drug delivery. Biotechnol Adv 32(7):1301–1316
43. Hu L, Sun Y, Wu Y (2013) Advances in chitosan-based drug delivery vehicles. Nanoscale 5(8):3103–3111
44. Kumar MNR (2000) A review of chitin and chitosan applications. React Funct Polym 46(1):1–27
45. Agnihotri SA, Mallikarjuna NN, Aminabhavi TM (2004) Recent advances on chitosan-based micro-and nanoparticles in drug delivery. J Control Release 100(1):5–28
46. Park BK, Kim MM (2010) Applications of chitin and its derivatives in biological medicine. Int J Mol Sci 11(12):5152–5164
47. Prabaharan M, Mano J (2004) Chitosan-based particles as controlled drug delivery systems. Drug Deliv 12(1):41–57
48. Jayakumar R, Menon D, Manzoor K, Nair SV, Tamura H (2010) Biomedical applications of chitin and chitosan based nanomaterials—a short review. Carbohydr Polym 82(2):227–232
49. McKenzie M, Betts D, Suh A, Bui K, Kim LD, Cho H (2015) Hydrogel-based drug delivery systems for poorly water-soluble drugs. Molecules 20(11):20397–20408
50. Win PP, Shin-Ya Y, Hong K-J, Kajiuchi T (2003) Formulation and characterization of pH sensitive drug carrier based on phosphorylated chitosan (PCS). Carbohydr Polym 53(3):305–310
51. Ahmadi F, Oveisi Z, Samani SM, Amoozgar Z (2015) Chitosan based hydrogels: characteristics and pharmaceutical applications. Res Pharm Sci 10(1):1
52. Berger J, Reist M, Mayer JM, Felt O, Peppas N, Gurny R (2004) Structure and interactions in covalently and ionically crosslinked chitosan hydrogels for biomedical applications. Eur J Pharm Biopharm 57(1):19–34
53. Moon RJ, Martini A, Nairn J, Simonsen J, Youngblood J (2011) Cellulose nanomaterials review: structure, properties and nanocomposites. Chem Soc Rev 40(7):3941–3994
54. Plackett D, Letchford K, Jackson J, Burt H (2014) A review of nanocellulose as a novel vehicle for drug delivery. Nordic Pulp Pap Res J 29(1):105–118
55. Sanga Pachuau L (2015) A mini review on plant-based nanocellulose: production, sources, modifications and its potential in drug delivery applications. Mini-reviews Med Chem 15(7):543–552
56. Abeer MM, Mohd Amin MCI, Martin C (2014) A review of bacterial cellulose-based drug delivery systems: their biochemistry, current approaches and future prospects. J Pharm Pharmacol 66(8):1047–1061
57. Jorfi M, Foster EJ (2015) Recent advances in nanocellulose for biomedical applications. J Appl Polym Sci 132(14):41719
58. Helenius G, Bäckdahl H, Bodin A, Nannmark U, Gatenholm P, Risberg B (2006) In vivo biocompatibility of bacterial cellulose. J Biomed Mater Res A 76(2):431–438
59. Xie J, Li J (2017) Smart drug delivery system based on nanocelluloses. J Bioresour Bioprod 2(1):1–3
60. Moritz S, Wiegand C, Wesarg F, Hessler N, Müller FA, Kralisch D, Hipler U-C, Fischer D (2014) Active wound dressings based on bacterial nanocellulose as drug delivery system for octenidine. Int J Pharm 471(1–2):45–55
61. Lam E, Male KB, Chong JH, Leung AC, Luong JH (2012) Applications of functionalized and nanoparticle-modified nanocrystalline cellulose. Trends Biotechnol 30(5):283–290
62. Almeida I, Pereira T, Silva N, Gomes F, Silvestre A, Freire C, Lobo JS, Costa P (2014) Bacterial cellulose membranes as drug delivery systems: an in vivo skin compatibility study. Eur J Pharm Biopharm 86(3):332–336
63. Panduranga Rao K (1996) Recent developments of collagen-based materials for medical applications and drug delivery systems. J Biomater Sci 7(7):623–645
64. Takezawa T, Takeuchi T, Nitani A, Takayama Y, Kino-Oka M, Taya M, Enosawa S (2007) Collagen vitrigel membrane useful for paracrine assays in vitro and drug delivery systems in vivo. J Biotechnol 131(1):76–83
65. Sehgal PK, Srinivasan A (2009) Collagen-coated microparticles in drug delivery. Expert Opin Drug Deliv 6(7):687–695
66. Vashist A, Vashist A, Gupta Y, Ahmad S (2014) Recent advances in hydrogel-based drug delivery systems for the human body. J Mater Chem B 2(2):147–166
67. Lee CH, Singla A, Lee Y (2001) Biomedical applications of collagen. Int J Pharm 221(1–2):1–22
68. Sahithi B, Ansari S, Hameeda S, Sahithya G, Prasad DM, Lakshmi Y (2013) A review on collagen based drug delivery systems. Ind J Res Pharm Biotechnol 1(3):461
69. Tamboli V, Patel S, Mishra GP, Mitra AK (2013) Biodegradable polymers for ophthalmic applications. In: Mitra AK (ed) Treatise on ocular drug delivery. Bentham Science, Sharjah, pp 96–113
70. Soppimath KS, Aminabhavi TM, Dave AM, Kumbar SG, Rudzinski W (2002) Stimulus-responsive "smart" hydrogels as novel drug delivery systems. Drug Dev Ind Pharm 28(8):957–974
71. Galaev IY, Mattiasson B (1999) 'Smart'polymers and what they could do in biotechnology and medicine. Trends Biotechnol 17(8):335–340
72. Motornov M, Tam TK, Pita M, Tokarev I, Katz E, Minko S (2009) Switchable selectivity for gating ion transport with mixed polyelectrolyte brushes: approaching 'smart'drug delivery systems. Nanotechnol 20(43):434006
73. Bawa P, Pillay V, Choonara YE, Du Toit LC (2009) Stimuli-responsive polymers and their applications in drug delivery. Biomed Mater 4(2):022001
74. Pötzinger Y, Kralisch D, Fischer D (2017) Bacterial nanocellulose: the future of controlled drug delivery? Ther Deliv 8(9):753–761
75. Xue Y, Mou Z, Xiao H (2017) Nanocellulose as a sustainable biomass material: structure, properties, present status and future prospects in biomedical applications. Nanoscale 9(39):14758–14781
76. Golieskardi M, Satgunam M, Ragurajan D, Hoque ME, Ng AMH, Shanmuganantha L (2019) Advanced 3Y-TZP bioceramic doped with Al_2O_3 and CeO_2 potentially for biomedical implant applications. Mater Technol 34(8):480–489
77. Hoque ME, Chuan YL, Pashby I, Aini SS, Hwei AMN, Idrus R (2014) Hybrid and single design scaffolds for new generation tissue engineering applications. Adv Sci Eng Med 6(1):92–96
78. Hoque M, Prasad R (2013) Rapid prototyping technology in bone tissue engineering. J Appl Mech Eng 2:124
79. Collignon AM, Rochefort GY (2018) Tissue engineering strategies to promote bone repair. Mater Sci Forum 941:2495–2500
80. Trieu H, Sherman M (2010) Collagen-based materials and methods for treating synovial joints. Google Pat 7(731):981
81. Zhou X (2018) Genipin-cross-linked type II collagen scaffold promotes the differentiation of adipose-derived stem cells into nucleus pulposus-like cells. J Biomed Mater Res A 106(5):1258–1268
82. Brückner T, Gbureck U (2017) Nano-magnesium phosphate hydrogels: efficiency of an injectable and biodegradable gel formulation towards bone regeneration. AME Med J 2(5):1–4
83. Pinese C, Gagnieu C, Nottelet B, Rondot-Couzin C, Hunger S, Coudane J, Garric X (2017) In vivo evaluation of hybrid patches composed of PLA based copolymers and collagen/chondroitin sulfate for ligament tissue regeneration. J Biomed Mater Res B 105(7):1778–1788

84. Silver FH, Kato YP (2019) Synthetic collagen orthopaedic structures such as grafts, tendons and other structures. Google Pat 5(171):273
85. Camenzind RS, Wieser K, Fessel G, Meyer DC, Snedeker JG (2016) Tendon collagen crosslinking offers potential to improve suture pullout in rotator cuff repair: an ex vivo sheep study. Clin Orthop Relat Res 474(8):1778–1785
86. Mozdzen LC, Rodgers R, Banks JM, Bailey RC, Harley BA (2016) Increasing the strength and bioactivity of collagen scaffolds using customizable arrays of 3D-printed polymer fibers. Acta Biomater 33:25–33
87. Hadidi P, Cissell DD, Hu JC, Athanasiou KA (2017) Temporal development of near-native functional properties and correlations with qMRI in self-assembling fibrocartilage treated with exogenous lysyl oxidase homolog 2. Acta Biomater 64:29–40
88. Nawae S, Meesane J, Muensit N, Daengngam C (2018) Layer-by-layer self-assembled films of silk fibroin/collagen/poly (diallyldimethylammonium chloride) as nucleating surface for osseointegration to design coated dental implant materials. Mater Des 160:1158–1167
89. Pighinelli L, Kucharska M (2013) Chitosan–hydroxyapatite composites. Carbohydr Polym 93(1):256–262
90. Babensee JE, Anderson JM, McIntire LV, Mikos AG (1998) Host response to tissue engineered devices. Adv Drug Del Rev 33(1):111–139
91. Hutmacher DW (2000) Scaffolds in tissue engineering bone and cartilage. Biomaterials 21(24):2529–2543
92. Ragurajan D, Golieskardi M, Satgunam M, Hoque ME, Ng AMH, Ghazali MJ, Ariffin AK (2018) Advanced 3Y-TZP bioceramic doped with Al2O3 and MnO2 particles potentially for biomedical applications: study on mechanical and degradation properties. J Mater Res Technol 7(4):432–442
93. Yu Z, An B, Ramshaw JA, Brodsky B (2014) Bacterial collagen-like proteins that form triple-helical structures. J Struct Biol 186(3):451–461
94. Friess W, Schlapp M (2006) Sterilization of gentamicin containing collagen/PLGA microparticle composites. Eur J Pharm Biopharm 63(2):176–187
95. Wu W, Feng X, Mao T, Feng X, Ouyang H-W, Zhao G, Chen F (2007) Engineering of human tracheal tissue with collagen-enforced poly-lactic-glycolic acid non-woven mesh: a preliminary study in nude mice. Br J Oral Maxillofac Surg 45(4):272–278
96. O'Brien FJ (2011) Biomaterials & scaffolds for tissue engineering. Mater Today 14(3):88–95
97. Chen C, Zhao ML, Zhang RK, Lu G, Zhao CY, Fu F, Sun HT, Zhang S, Tu Y, Li XH (2017) Collagen/heparin sulfate scaffolds fabricated by a 3D bioprinter improved mechanical properties and neurological function after spinal cord injury in rats. J Biomed Mater Res A 105(5):1324–1332
98. Ryan AJ, Lackington WA, Hibbitts AJ, Matheson A, Alekseeva T, Stejskalova A, Roche P, O'Brien FJ (2017) A physicochemically optimized and neuroconductive biphasic nerve guidance conduit for peripheral nerve repair. Adv Healthc Mater 6(24):1700954
99. Pawelec KM, Confalonieri D, Ehlicke F, van Boxtel HA, Walles H, Kluijtmans SG (2017) Osteogenesis and mineralization of mesenchymal stem cells in collagen type I-based recombinant peptide scaffolds. J Biomed Mater Res A 105(7):1856–1866
100. Versteegden LR, Van Kampen KA, Janke HP, Tiemessen DM, Hoogenkamp HR, Hafmans TG, Roozen EA, Lomme RM, van Goor H, Oosterwijk E, Feitz WF (2017) Tubular collagen scaffolds with radial elasticity for hollow organ regeneration. Acta Biomater 52:1–8
101. Lee JC, Pereira CT, Ren X, Huang W, Bischoff D, Weisgerber DW, Yamaguchi DT, Harley BA, Miller TA (2015) Optimizing collagen scaffolds for bone engineering: effects of cross-linking and mineral content on structural contraction and osteogenesis. J Craniofac Surg 26(6):1992
102. Mitra D, Yasui OW, Harvestine JN, Link JM, Hu JC, Athanasiou KA, Leach JK (2019) Exogenous lysyl oxidase-Like 2 and perfusion culture induce collagen crosslink formation in osteogenic grafts. Biotechnol J 14(3):1700763
103. Zhang Y, Venugopal JR, El-Turki A, Ramakrishna S, Su B, Lim CT (2008) Electrospun biomimetic nanocomposite nanofibers of hydroxyapatite/chitosan for bone tissue engineering. Biomaterials 29(32):4314–4322
104. Di Martino A, Sittinger M, Risbud MV (2005) Chitosan: a versatile biopolymer for orthopaedic tissue-engineering. Biomaterials 26(30):5983–5990
105. Miroiu FM, Socol G, Visan A, Stefan N, Craciun D, Craciun V, Dorcioman G, Mihailescu IN, Sima LE, Petrescu SM, Andronie A (2010) Composite biocompatible hydroxyapatite–silk fibroin coatings for medical implants obtained by matrix assisted pulsed laser evaporation. Mater Sci Eng B 169(1–3):151–158
106. Lin HR, Yeh YJ (2004) Porous alginate/hydroxyapatite composite scaffolds for bone tissue engineering: preparation, characterization, and in vitro studies. J Biomed Mater Res B 71(1):52–65
107. Sadjadi MS, Meskinfam M, Sadeghi B, Jazdarreh H, Zare K (2010) In situ biomimetic synthesis, characterization and in vitro investigation of bone-like nanohydroxyapatite in starch matrix. Mater Chem Phys 124(1):217–222
108. Li J, Baker BA, Mou X, Ren N, Qiu J, Boughton RI, Liu H (2014) Biopolymer/calcium phosphate scaffolds for bone tissue engineering. Adv Healthc Mater 3(4):469–484
109. Osorio DA, Lee BE, Kwiecien JM, Wang X, Shahid I, Hurley AL, Cranston ED, Grandfield K (2019) Cross-linked cellulose nanocrystal aerogels as viable bone tissue scaffolds. Acta Biomater 87:152–165
110. Gleeson JP, Plunkett NA, O'Brien FJ (2010) Addition of hydroxyapatite improves stiffness, interconnectivity and osteogenic potential of a highly porous collagen-based scaffold for bone tissue regeneration. Eur Cell Mater 20:218–230
111. Catledge SA, Clem WC, Shrikishen N, Chowdhury S, Stanishevsky AV, Koopman M, Vohra YK (2007) An electrospun triphasic nanofibrous scaffold for bone tissue engineering. Biomed Mater 2(2):142
112. Sionkowska A, Kozłowska J (2013) Properties and modification of porous 3-D collagen/hydroxyapatite composites. Int J Biol Macromol 52:250–259
113. Al-Munajjed AA, Plunkett A, Gleeson JP, Weber T, Jungreuthmayer C, Levingstone T, Hammer J, O'Brien FJ (2009) Development of a biomimetic collagen-hydroxyapatite scaffold for bone tissue engineering using a SBF immersion technique. J Biomed Mater Res B 90(2):584–591
114. Elkin BS, Azeloglu EU, Costa KD, Morrison B (2007) Mechanical heterogeneity of the rat hippocampus measured by atomic force microscope indentation. J Neurotrauma 24(5):812–822
115. Levental I, Georges PC, Janmey PA (2007) Soft biological materials and their impact on cell function. Soft Matter 3(3):299–306
116. Yousefi AM, Hoque ME, Prasad RG, Uth N (2015) Current strategies in multiphasic scaffold design for osteochondral tissue engineering: a review. J Biomed Mater Res A 103(7):2460–2481
117. Fu W, Liu Z, Feng B, Hu R, He X, Wang H, Yin M, Huang H, Zhang H, Wang W (2014) Electrospun gelatin/PCL and collagen/PLCL scaffolds for vascular tissue engineering. Int J Nanomed 9:2335
118. Vatankhah E, Prabhakaran MP, Semnani D, Razavi S, Morshed M, Ramakrishna S (2014) Electrospun tecophilic/gelatin nanofibers with potential for small diameter blood vessel tissue engineering. Biopolym 101(12):1165–1180

119. de Souza RF, de Souza FC, Rodrigues C, Drouin B, Popat KC, Mantovani D, Moraes ÂM (2019) Mechanically-enhanced polysaccharide-based scaffolds for tissue engineering of soft tissues. Mater Sci Eng C 94:364–375
120. Montalbano G, Toumpaniari S, Popov A, Duan P, Chen J, Dalgarno K, Scott WE III, Ferreira AM (2018) Synthesis of bioinspired collagen/alginate/fibrin-based hydrogels for soft tissue engineering. Mater Sci Eng C 91:236–246
121. Hasan MM, Khan MN, Haque P, Rahman MM (2018) Novel alginate-di-aldehyde cross-linked gelatin/nano-hydroxyapatite bioscaffolds for soft tissue regeneration. Int J Biol Macromol 117:1110–1117
122. Gomes S, Rodrigues G, Martins G, Henriques C, Silva JC (2017) Evaluation of nanofibrous scaffolds obtained from blends of chitosan, gelatin and polycaprolactone for skin tissue engineering. Int J Biol Macromol 102:1174–1185
123. Vieira T, Silva JC, Borges JP, Henriques C (2018) Synthesis, electrospinning and in vitro test of a new biodegradable gelatin-based poly (ester urethane urea) for soft tissue engineering. Eur Polym J 103:271–281
124. Silva R, Singh R, Sarker B, Papageorgiou DG, Juhasz-Bortuzzo JA, Roether JA, Cicha I, Kaschta J, Schubert DW, Chrissafis K, Detsch R (2018) Hydrogel matrices based on elastin and alginate for tissue engineering applications. Int J Biol Macromol 114:614–625
125. Vogt L, Liverani L, Roether JA, Boccaccini AR (2018) Electrospun zein fibers incorporating poly (glycerol sebacate) for soft tissue engineering. Nanomaterials 8(3):150
126. Little CJ, Kulyk WM, Chen X (2014) The effect of chondroitin sulphate and hyaluronic acid on chondrocytes cultured within a fibrin-alginate hydrogel. J Funct Biomater 5(3):197–210
127. Saadatkish N, Nouri Khorasani S, Morshed M, Allafchian AR, Beigi MH, Masoudi Rad M, Esmaeely Neisiany R, Nasr-Esfahani MH (2018) A ternary nanofibrous scaffold potential for central nerve system tissue engineering. J Biomed Mater Res A 106(9):2394–2401
128. Hasan A, Waibhaw G, Saxena V (2018) Pandey LM (2018) Nano-biocomposite scaffolds of chitosan, carboxymethyl cellulose and silver nanoparticle modified cellulose nanowhiskers for bone tissue engineering applications. Int J Biol Macromol 111:923–934
129. Isobe N, Komamiya T, Kimura S, Kim UJ, Wada M (2018) Cellulose hydrogel with tunable shape and mechanical properties: from rigid cylinder to soft scaffold. Int J Biol Macromol 117:625–631
130. Deepthi S, Jayakumar R (2018) Alginate nanobeads interspersed fibrin network as in situ forming hydrogel for soft tissue engineering. Bioact Mater 3(2):194–200
131. Hirsch T, Laemmle C, Behr B, Lehnhardt M, Jacobsen F, Hoefer D, Kueckelhaus M (2018) Implant for autologous soft tissue reconstruction using an adipose-derived stem cell-colonized alginate scaffold. J Plast Reconstr Aesthet Surg 71(1):101–111
132. Xu Y, Liang K, Ullah W, Ji Y, Ma J (2018) Chitin nanocrystal enhanced wet adhesion performance of mussel-inspired citrate-based soft-tissue adhesive. Carbohydr Polym 190:324–330
133. Gámiz-González M, Vidaurre A, Ribelles JG (2017) Biodegradable chitosan-poly (Ɛ-caprolactone) dialdehyde copolymer networks for soft tissue engineering. Polym Degrad Stab 138:47–54
134. Nikpour P, Salimi-Kenari H, Fahimipour F, Rabiee SM, Imani M, Dashtimoghadam E, Tayebi L (2018) Dextran hydrogels incorporated with bioactive glass-ceramic: nanocomposite scaffolds for bone tissue engineering. Carbohydr Polym 190:281–294
135. Tamayo L, Acuña D, Riveros AL, Kogan MJ, Azocar MI, Páez M, Leal M, Urzúa M, Cerda E (2018) Porous nanogold/polyurethane scaffolds with improved antibiofilm, mechanical, and thermal properties and with reduced effects on cell viability: a suitable material for soft tissue applications. ACS Appl Mater Interface 10(16):13361–13372
136. Kucińska-Lipka J, Gubańska I, Janik H (2013) Gelatin-modified polyurethanes for soft tissue scaffold. Sci World J 2013:1–12
137. Kundu S, Das A, Basu A, Ghosh D, Datta P, Mukherjee A (2018) Carboxymethyl guar gum synthesis in homogeneous phase and macroporous 3D scaffolds design for tissue engineering. Carbohydr Polym 191:71–78
138. Hoque ME, Meng TT, Chuan YL, Chowdhury M, Prasad RG (2014) Fabrication and characterization of hybrid PCL/PEG 3D scaffolds for potential tissue engineering applications. Mater Lett 131:255–258
139. Vedadghavami A, Minooei F, Mohammadi MH, Khetani S, Kolahchi AR, Mashayekhan S, Sanati-Nezhad A (2017) Manufacturing of hydrogel biomaterials with controlled mechanical properties for tissue engineering applications. Acta Biomater 62:42–63
140. Saldin LT, Cramer MC, Velankar SS, White LJ, Badylak SF (2017) Extracellular matrix hydrogels from decellularized tissues: structure and function. Acta Biomater 49:1–15
141. Grant SA, Zhu J, Gootee J, Snider CL, Bellrichard M, Grant DA (2018) Gold nanoparticle-collagen gels for soft tissue augmentation. Tissue Eng A 24(13–14):1091–1098
142. Ramanathan G, Singaravelu S, Raja MD, Nagiah N, Padmapriya P, Ruban K, Kaveri K, Natarajan TS, Sivagnanam UT, Perumal PT (2016) Fabrication and characterization of a collagen coated electrospun poly (3-hydroxybutyric acid)–gelatin nanofibrous scaffold as a soft bio-mimetic material for skin tissue engineering applications. RSC Adv 6(10):7914–7922
143. Tangsadthakun C, Kanokpanont S, Sanchavanakit N, Banaprasert T, Damrongsakkul S (2017) Properties of collagen/chitosan scaffolds for skin tissue engineering. J Met Mater Miner 16(1):37–44
144. Rhee S, Puetzer JL, Mason BN, Reinhart-King CA, Bonassar LJ (2016) 3D bioprinting of spatially heterogeneous collagen constructs for cartilage tissue engineering. ACS Biomater Sci Eng 2(10):1800–1805
145. Kumar VA, Martinez AW, Caves JM, Naik N, Haller CA, Chaikof EL (2014) Microablation of collagen-based substrates for soft tissue engineering. Biomed Mater 9(1):011002
146. Meghezi S, Seifu DG, Bono N, Unsworth L, Mequanint K, Mantovani D (2015) Engineering 3D cellularized collagen gels for vascular tissue regeneration. J Vis Exp 100:1–12
147. Long K, Liu Y, Li W, Wang L, Liu S, Wang Y, Wang Z, Ren L (2015) Improving the mechanical properties of collagen-based membranes using silk fibroin for corneal tissue engineering. J Biomed Mater Res A 103(3):1159–1168
148. Hoque ME, Nuge T, Yeow TK, Nordin N, Prasad RG (2015) Gelatin based scaffolds for tissue engineering-a review. Polym Res J 9(1):15
149. Contessi Negrini N, Tarsini P, Tanzi MC, Farè S (2018) Chemically crosslinked gelatin hydrogels as scaffolding materials for adipose tissue engineering. J Appl Polym Sci 136(8):47104
150. Sharma A, Bhat S, Nayak V, Kumar A (2015) Efficacy of supermacroporous poly (ethylene glycol)–gelatin cryogel matrix for soft tissue engineering applications. Mater Sci Eng C 47:298–312
151. Nadim A, Khorasani SN, Kharaziha M, Davoodi SM (2017) Design and characterization of dexamethasone-loaded poly (glycerol sebacate)-poly caprolactone/gelatin scaffold by coaxial electro spinning for soft tissue engineering. Mater Sci Eng C 78:47–58
152. Daniele MA, Adams AA, Naciri J, North SH, Ligler FS (2014) Interpenetrating networks based on gelatin methacrylamide and PEG formed using concurrent thiol click chemistries for hydrogel tissue engineering scaffolds. Biomaterials 35(6):1845–1856

153. Radaei P, Mashayekhan S, Vakilian S (2017) Modeling and optimization of gelatin-chitosan micro-carriers preparation for soft tissue engineering: using response surface methodology. Mater Sci Eng C 75:545–553
154. Dai X, Kathiria K, Huang YC (2014) Electrospun fiber scaffolds of poly (glycerol-dodecanedioate) and its gelatin blended polymers for soft tissue engineering. Biofabrication 6(3):035005
155. Pesqueira T, Costa-Almeida R, Mithieux SM, Babo PS, Franco AR, Mendes BB, Domingues RM, Freitas P, Reis RL, Gomes ME, Weiss AS (2018) Engineering magnetically responsive tropoelastin spongy-like hydrogels for soft tissue regeneration. J Mater Chem B 6(7):1066–1075
156. Markstedt K, Mantas A, Tournier I, Martínez Ávila H, Hagg D, Gatenholm P (2015) 3D bioprinting human chondrocytes with nanocellulose–alginate bioink for cartilage tissue engineering applications. Biomacromol 16(5):1489–1496
157. Almeida HV, Sathy BN, Dudurych I, Buckley CT, O'Brien FJ, Kelly DJ (2017) Anisotropic shape-memory alginate scaffolds functionalized with either type I or type II collagen for cartilage tissue engineering. Tissue Eng A 23(1–2):55–68
158. Yuan L, Wu Y, Fang J, Wei X, Gu Q, El-Hamshary H, Al-Deyab SS, Morsi Y, Mo X (2017) Modified alginate and gelatin cross-linked hydrogels for soft tissue adhesive. Artif Cells Nanomed Biotechnol 45(1):76–83
159. Jaikumar D, Sajesh KM, Soumya S, Nimal TR, Chennazhi KP, Nair SV, Jayakumar R (2015) Injectable alginate-O-carboxymethyl chitosan/nano fibrin composite hydrogels for adipose tissue engineering. Int J Biol Macromol 74:318–326
160. Ceccaldi C, Bushkalova R, Cussac D, Duployer B, Tenailleau C, Bourin P, Parini A, Sallerin B, Fullana SG (2017) Elaboration and evaluation of alginate foam scaffolds for soft tissue engineering. Int J Pharm 524(1–2):433–442
161. Yang S, Jang L, Kim S, Yang J, Yang K, Cho SW, Lee JY (2016) Polypyrrole/alginate hybrid hydrogels: electrically conductive and soft biomaterials for human mesenchymal stem cell culture and potential neural tissue engineering applications. Macromol Biosci 16(11):1653–1661
162. Shefy-Peleg A, Foox M, Cohen B, Zilberman M (2014) Novel antibiotic-eluting gelatin-alginate soft tissue adhesives for various wound closing applications. Int J Polym Mater 63(14):699–707
163. Barikani M, Honarkar H, Barikani M (2009) Synthesis and characterization of polyurethane elastomers based on chitosan and poly (ε-caprolactone). J Appl Polym Sci 112(5):3157–3165
164. Oliveira JM, Rodrigues MT, Silva SS, Malafaya PB, Gomes ME, Viegas CA, Dias IR, Azevedo JT, Mano JF, Reis RL (2006) Novel hydroxyapatite/chitosan bilayered scaffold for osteochondral tissue-engineering applications: scaffold design and its performance when seeded with goat bone marrow stromal cells. Biomaterials 27(36):6123–6137
165. Fan M, Ma Y, Mao J, Zhang Z, Tan H (2015) Cytocompatible in situ forming chitosan/hyaluronan hydrogels via a metal-free click chemistry for soft tissue engineering. Acta Biomater 20:60–68
166. Kanimozhi K, Basha SK, Kumari VS, Kaviyarasu K, Maaza M (2018) In vitro cytocompatibility of chitosan/PVA/methylcellulose–nanocellulose nanocomposites scaffolds using L929 fibroblast cells. Appl Surf Sci 449:574–583
167. Jung KH, Huh MW, Meng W, Yuan J, Hyun SH, Bae JS, Hudson SM, Kang IK (2007) Preparation and antibacterial activity of PET/chitosan nanofibrous mats using an electrospinning technique. J Appl Polym Sci 105(5):2816–2823
168. Zhou Y, Liang K, Zhao S, Zhang C, Li J, Yang H, Liu X, Yin X, Chen D, Xu W, Xiao P (2018) Photopolymerized maleilated chitosan/methacrylated silk fibroin micro/nanocomposite hydrogels as potential scaffolds for cartilage tissue engineering. Int J Biol Macromol 108:383–390
169. Kamoun EA, Kenawy ERS, Chen X (2017) A review on polymeric hydrogel membranes for wound dressing applications: PVA-based hydrogel dressings. J Adv Res 8(3):217–233
170. Pomahač B, Svensjö T, Yao F, Brown H, Eriksson E (1998) Tissue engineering of skin. Crit Rev Oral Biol Med 9(3):333–344
171. Zhong SP, Zhang YZ, Lim CT (2010) Tissue scaffolds for skin wound healing and dermal reconstruction. Nanomed Nanobiotechnol 2(5):510–525
172. Boateng JS, Matthews KH, Stevens HN, Eccleston GM (2008) Wound healing dressings and drug delivery systems: a review. J Pharm Sci 97(8):2892–2923
173. Dreifke MB, Jayasuriya AA, Jayasuriya AC (2015) Current wound healing procedures and potential care. Mater Sci Eng C 48:651–662
174. Velnar T, Bailey T, Smrkolj V (2009) The wound healing process: an overview of the cellular and molecular mechanisms. J Int Med Res 37(5):1528–1542
175. Korting H, Schöllmann C, White R (2011) Management of minor acute cutaneous wounds: importance of wound healing in a moist environment. J Eur Acad Dermatol Venereol 25(2):130–137
176. Moore K, McCallion R, Searle RJ, Stacey MC, Harding KG (2006) Prediction and monitoring the therapeutic response of chronic dermal wounds. Int Wound J 3(2):89–98
177. Zahedi P, Rezaeian I, Ranaei-Siadat SO, Jafari SH, Supaphol P (2010) A review on wound dressings with an emphasis on electrospun nanofibrous polymeric bandages. Polym Adv Technol 21(2):77–95
178. Harding KG, Morris HL, Patel GK (2002) Healing chronic wounds. BMJ 324(7330):160–163
179. Percival NJ (2002) Classification of wounds and their management. Surg 20(5):114–117
180. Witte MB, Barbul A (1997) General principles of wound healing. Surg Clin North Am 77(3):509–528
181. Young A, McNaught CE (2011) The physiology of wound healing. Surg 29(10):475–479
182. Hunt TK (1988) The physiology of wound healing. Ann Emerg Med 17(12):1265–1273
183. Jayakumar R, Prabaharan M, Kumar PS, Nair SV, Tamura H (2011) Biomaterials based on chitin and chitosan in wound dressing applications. Biotechnol Adv 29(3):322–337
184. Smith AM, Moxn S, Morris GA (2016) Biopolymers as wound healing materials. Wound Heal Biomater. https://doi.org/10.1016/B978-1-78242-456-7.00013-1
185. Laurienzo P (2010) Marine polysaccharides in pharmaceutical applications: an overview. Mar Drugs 8(9):2435–2465
186. Sahana T, Rekha P (2018) Biopolymers: applications in wound healing and skin tissue engineering. Mol Biol Rep 45(6):2857–2867
187. Das N, Bera T, Mukherjee A (2012) Biomaterial hydrogels for different biomedical applications. Int J Pharm Bio Sci 3(3):586-P595
188. Knapp TR, Kaplan EN, Daniels JR (1977) Injectable collagen for soft tissue augmentation. Plast Reconstr Surg 60(3):398–405
189. Mogoşanu GD, Grumezescu AM (2014) Natural and synthetic polymers for wounds and burns dressing. Int J Pharm 463(2):127–136
190. Sailakshmi G, Mitra T, Gnanamani A, Raja ST, Thiruselvi T, Selvaraj NV, Ramesh G, Mandal AB (2011) Bonding interactions and stability assessment of biopolymer material prepared using type III collagen of avian intestine and anionic polysaccharides. J Mater Sci Mater Med 22(6):1419–1429
191. Trombino S, Cassano R, Ferrarelli T, Isacchi B, Bilia AR, Picci N (2012) Collagen α-tocopherulate for topical applications:

preparation, characterization, and antioxidant activity evaluation. Macromol Res 20(9):939–943
192. Fullana MJ, Wnek GE (2012) Electrospun collagen and its applications in regenerative medicine. Drug Deliv Transl Res 2(5):313–322
193. Kempf M, Miyamura Y, Liu PY, Chen AC, Nakamura H, Shimizu H, Tabata Y, Kimble RM, McMillan JR (2011) A denatured collagen microfiber scaffold seeded with human fibroblasts and keratinocytes for skin grafting. Biomaterials 32(21):4782–4792
194. Ghica MV, Albu MG, Leca M, Popa L, Moisescu ST (2011) Design and optimization of some collagen-minocycline based hydrogels potentially applicable for the treatment of cutaneous wound infections. Pharmazie 66(11):853–861
195. Roussille G, Barthet B (1991) Evaluation of a collagen-glycosaminoglycan complex as a dressing for gingival wounds. J Mater Sci Mater Med 2(4):208–211
196. Sedlarik KM, Schoots C, Oosterbaan JA, Klopper JP (1992) The wound healing of a full thickness wound in guinea pigs by the use of collagen sponge as a wound dressing. Aktuelle Traumatol 22(5):219–228
197. Croisier F, Jérôme C (2013) Chitosan-based biomaterials for tissue engineering. Eur Polym J 49(4):780–792
198. Blasinska A, Drobnik J (2008) Effects of nonwoven mats of Di-O-butyrylchitin and related polymers on the process of wound healing. Biomacromolecules 9(3):776–782
199. Berger J, Reist M, Mayer JM, Felt O, Gurny R (2004) Structure and interactions in chitosan hydrogels formed by complexation or aggregation for biomedical applications. Eur J Pharm Biopharm 57(1):35–52
200. Cascone MG, Maltinti S, Barbani N, Laus M (1999) Effect of chitosan and dextran on the properties of poly(vinyl alcohol) hydrogels. J Mater Sci Mater Med 10(7):431–435
201. Seol YJ, Lee JY, Park YJ, Lee YM, Rhyu IC, Lee SJ, Han SB, Chung CP (2004) Chitosan sponges as tissue engineering scaffolds for bone formation. Biotechnol Lett 26(13):1037–1041
202. Peh K, Khan T, Ch'ng H (2000) Mechanical, bioadhesive strength and biological evaluations of chitosan films for wound dressing. J Pharm Pharm Sci 3(3):303–311
203. Huang XJ, Ge D, Xu JK (2007) Preparation and characterization of stable chitosan nanofibrous membrane for lipase immobilization. Eur Polym J 43(9):3710–3718
204. Duan B, Yuan X, Zhu Y, Zhang Y, Li X, Zhang Y, Yao KA (2006) A nanofibrous composite membrane of PLGA–chitosan/PVA prepared by electrospinning. Eur Polym J 42(9):2013–2022
205. Jones V, Grey JE, Harding KG (2006) Wound dressings. BMJ 332(7544):777–780
206. Lu Y, Biswas MC, Guo Z, Jeon JW, Wujcik EK (2019) Recent developments in bio-monitoring via advanced polymer nanocomposite-based wearable strain sensors. Biosens Bioelectron 123:167–177
207. Hernández-Ibáñez N, García-Cruz L, Montiel V, Foster CW, Banks CE, Iniesta J (2016) Electrochemical lactate biosensor based upon chitosan/carbon nanotubes modified screen-printed graphite electrodes for the determination of lactate in embryonic cell cultures. Biosens Bioelectron 77:1168–1174
208. Chang J, Xiao W, Liu P, Liao X, Wen Y, Bai L, Li L, Li M (2016) Carboxymethyl cellulose assisted preparation of water-processable halloysite nanotubular composites with carboxyl-functionalized multi-carbon nanotubes for simultaneous voltammetric detection of uric acid, guanine and adenine in biological samples. J Electroanal Chem 780:103–113
209. Crouzier T, Boudou T, Picart C (2010) Polysaccharide-based polyelectrolyte multilayers. Curr Opin Colloid Interface Sci 15(6):417–426
210. Eiras C, Santos AC, Zampa MF, de Brito AC, Leopoldo Constantino CJ, Zucolotto V, dos Santos JR (2010) Natural polysaccharides as active biomaterials in nanostructured films for sensing. J Biomater Sci 21(11):1533–1543
211. Cannatelli MD, Ragauskas AJ (2017) Two decades of laccases: advancing sustainability in the chemical industry. Chem Rec 17(1):122–140
212. Sartori ER, Vicentini FC, Fatibello-Filho O (2011) Indirect determination of sulfite using a polyphenol oxidase biosensor based on a glassy carbon electrode modified with multi-walled carbon nanotubes and gold nanoparticles within a poly (allylamine hydrochloride) film. Talanta 87:235–242
213. Goodman LS (1996) Goodman and Gilman's the pharmacological basis of therapeutics. McGraw-Hill, New York, pp 127–132
214. Liu X, Shuai HL, Liu YJ, Huang KJ (2016) An electrochemical biosensor for DNA detection based on tungsten disulfide/multi-walled carbon nanotube composites and hybridization chain reaction amplification. Sens Actuators B 235:603–613
215. Onar N (2004) Usage of biopolymers in medical applications. In: Proc 3rd Indo-Czech Text Res Conf
216. Azimi B, Nourpanah P, Rabiee M, Arbab S (2014) Poly (lactide-co-glycolide) fiber: an overview. J Eng Fiber Fabr 9(1):155892501400900100
217. Pivsa-Art W, Chaiyasat A, Pivsa-Art S, Yamane H, Ohara H (2013) Preparation of polymer blends between poly (lactic acid) and poly (butylene adipate-co-terephthalate) and biodegradable polymers as compatibilizers. Energy Procedia 34:549–554
218. Shanks R, Kong I (2012) Thermoplastic Elastomers, 1st edn. Applied Sciences, RMIT University, Melbourne, pp 95–116
219. Panwiriyarat W (2013) Preparation and properties of biobased polyurethane made from natural rubber and poly (Ɛ-caprolactone). Prince of Songkla University
220. Maitz MF (2015) Applications of synthetic polymers in clinical medicine. Biosurf Biotribol 1(3):161–176
221. Bennet D, Kim S (2014) Polymer nanoparticles for smart drug delivery. Appl Nanotechnol Drug Deliv 25:257–310
222. Gaharwar AK, Arpanaei A, Andresen TL, Dolatshahi-Pirouz A (2016) 3D biomaterial microarrays for regenerative medicine: current state-of-the-art, emerging directions and future trends. Adv Mater 28(4):771–781
223. Kikuchi M, Koyama Y, Edamura K, Irie A, Sotome S, Itoh S, Takakuda K, Shinomiya K, Tanaka S (2011) Synthesis of hydroxyapatite/collagen bone-like nanocomposite and its biological reactions. Advances in nanocomposites-synthesis, characterization and industrial applications. Adv Nanocomposites—Synth Charact Ind Appl 2:181–194