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Scaffolding polymeric biomaterials: Are naturally occurring biological macromolecules more appropriate for tissue engineering?

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Contents

Abstract

Nowadays, tissue and organ failures resulted from injury, aging accounts, diseases or other type of damages is one of the most important health problems with an increasing incidence worldwide. Current treatments have limitations including, low graft efficiency, shortage of donor organs, as well as immunological problems. In this context, tissue engineering (TE) was introduced as a novel and versatile approach for restoring tissue/organ function using living cells, scaffold and bioactive (macro-)molecules. Among these, scaffold as a three-dimensional (3D) support material, provide physical and chemical cues for seeding cells and has an essential role in cell missions. Among the wide verity of scaffolding materials, natural or synthetic biopolymers are the most commonly biomaterials mainly due to their unique physicochemical and biological features. In this context, naturally occurring biological macromolecules are particular of interest owing to their low immunogenicity, excellent biocompatibility and cytocompatibility, as well as antigenicity that qualified them as popular choices for scaffolding applications. In this review, we highlighted the potentials of natural and synthetic polymers as scaffolding materials. The properties, advantages, and disadvantages of both polymer types as well as the current status, challenges, and recent progresses regarding the application of them as scaffolding biomaterials are also discussed.

Keywords: Natural polymers, Synthetic polymers, Modification, Polymer blends, Scaffold, Tissue engineering

1. Introduction

At the current time, failure of tissue and organ function resulted from injury, diseases or another type of damages is one of the most important health issues. Some treatment methods including, mechanical devices, surgical repair, drug therapy, artificial prostheses, and transplantation (human or xenotransplantation) have been employed in circumventing these health problems. However, the repair or regeneration of failed tissue/organ by these approaches are not satisfactory in all cases. For example, it has been well established that a damaged neuronal tissue does not regenerate. Because neuronal tissue did not contain any stem cells, and therefore would not self-regenerate [1-4]. In this context, tissue engineering (TE) is emerging as a novel and powerful alternative for above-mentioned approaches for repair or regeneration of a failed tissue/organ. This approach combines engineering, chemistry, molecular biology, as well as materials sciences for repairing or replacement of failed tissues/organs using living cells, scaffold, and signal molecules as the three key fundamental elements. Among these, the scaffold provides physical and chemical cues for seeding cells and has an essential role in their missions such as adherence, proliferation, and differentiation [5-8]. In addition, scaffolding biomaterials can be engineered to mobilize and present biologically active signal molecules such as cell homing factors and numerous growth/differentiation and mechanical signals in order to enhance the proliferation as well as differentiation of seeded cells and finally, to direct *neo*-tissue formation and integration [9].

According to the scientist's opinion, the most important question which needs to be answered towards a successful TE is that: What kinds of cells, bioactive (macro-)molecules, and biomaterials are suitable for a successful TE? Among these, in this review, we highlighted the importance of biomaterials in the performance of a TE followed by discussion regarding the

potentials of naturally occurring biological macromolecules and synthetic polymers as scaffolding biomaterials. The properties, advantages, and disadvantages of both polymer types, as well as recent progresses in the design and development of scaffolding biomaterials using both types of polymeric materials will be discussed extensively.

2. Scaffolding biomaterials: Current status, challenges, and recent progresses

It is well documented that the scaffold support and foster regenerative cell growth and plays a pivotal role in the performance of a TE. The scaffolding biomaterial provides temporary three dimensional (3D) mechanical support and mass transport to encourage cell adhesion, proliferation, differentiation, and finally the formation of *neo*-tissue [2, 10, 11]. An ideal scaffold should mimic the biomechanical function, topological and microstructural characteristics of the native extracellular matrix (ECM). For this, the scaffold must possess some properties including, high surface-to-volume ratio, a high degree of porosity and pore interconnection (in order to support cell/tissue penetration), appropriate pore size, and geometry control. In addition, other characteristics of a suitable scaffold can be listed as proper cell-matrix interactions, good mechanical properties, appropriate chemical composition, excellent biocompatibility, acceptable biodegradation and catabolization rates, and simple and cost-effective fabrication technology [9, 11, 12]. Therefore, the design and development of scaffolding biomaterial are the important requirements of TE using implantable scaffolds. The demand for safer and more efficient products for biomedical applications encouraged material and polymer scientists as well as biologists to design and develop the novel functional and more effective biomaterials for scaffolding over past few decade. In this context, human origin biomaterials are the first choice as scaffolding biomaterials, mainly due to their superior physicochemical as well as biological features including, mimic the critical aspects of native ECM, provide physical and chemical cues

for wound healing and tissue regeneration, excellent biocompatibility, and autologous preparations rich in growth factors [2, 13]. These type of biomaterials is created through the elimination of all cellular and nuclear materials from native tissues or organs. However, the most important issue regarding these type of biomaterials is the limitation of sources. Among the alternation biomaterials for scaffolding, natural and synthetic polymers are considerable of interest due to their abundances as well as superior physicochemical and biological characteristics.

Despite the most advantages, both polymer types have various drawbacks that limit their applications for developing ideal scaffolds. Various physicochemical and biological advantages and disadvantages of both polymer types will be discussed in the corresponding sections. However, some important challenging issues regarding the use of natural and synthetic polymers as scaffolding biomaterials are highlighted in following.

The most important properties of natural polymers are bioactivity (that promote biological recognition such as proper cell adhesion and function), biocompatibility (that reduce or eliminate undesirable host responses), 3D geometry, tunable degradation kinetics and mechanical as well as solubility properties, antigenicity, non-toxic biodegradation by-products and the intrinsic structural resemblance to mimic the native ECM [12]. On the other hand, the most important disadvantages of natural polymers can be listed as generally weak mechanical strength and inconsistency in compositions and properties that associated with batch production due to their origin in living beings, rapid degradation kinetics, uncontrolled rate of hydration, resources limitation in some cases that lead to high cost, and microbial spoilage [14].

In contrast, synthetic polymers are easily produced on a large scale and relatively low cost in the most cases with controlled molecular weight and functionality. Despite these important advantages, the main drawback of synthetic polymers that restrict their application ranges in the field of biomedical (*e.g.,* regenerative medicine) is the lack of biological cues such as cell recognition signals (known as biocompatibility) as well as biodegradability in most cases [10]. The degradation by-products of some synthetic polymers such as poly(α-hydroxy esters) involves the acidic compounds that can alter the pH of their surrounding tissues. This pH change can affect cell behavior and survival and leds to adverse tissue and inflammatory reactions [15]. Lack of biologically active sites for binding regulatory peptides, growth factors and other biological signals that restrict the cells adhesion or direct phenotypic expression. Therefore, the design and development of the synthetic strategies for the incorporation of biologically active domains, define as an artificial *in vivo* milieu, into the synthetic polymers is necessary for enhance their quality as scaffolding biomaterials. In this context, co-electrospinning of synthetic polymers with collagen or serum coating as well as other biological modifications can enhance initial cell attachment and ECM deposition [16].

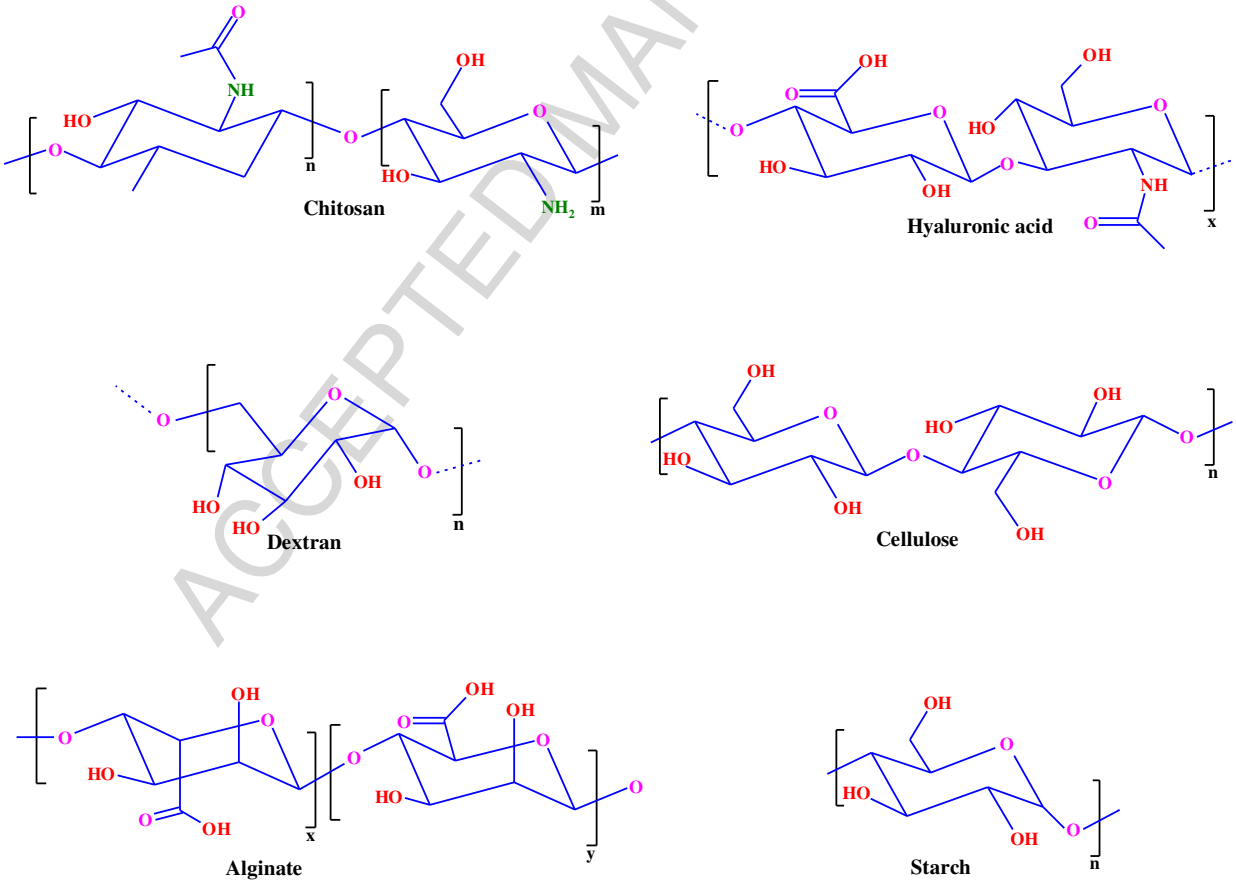
It is well documented that a single-component template does not meet the necessary requirements as a scaffolding biomaterial mainly due to a lack of a controlled degradation rate, a lack of proper mechanical properties and bioactivity, as well as a lack of the desired cell-matrix interactions to control gene expression, cytoskeletal structure and dynamics [17-19]. Therefore, modification of both natural and synthetic polymers using various chemical, physical as well as biological approaches or the use of multi-component biomaterials can be led to more desirable results [20-22]. In the following, the most important physicochemical as well as biological features of synthetic and natural polymers will be discussed. In addition, various strategies, as

well as recent progresses toward the scaffolding biomaterials, possess proper physicochemical and biological characteristics using modification (chemical, physical, and biological), mineralization, crosslinking and blending approaches in the field will be highlighted.

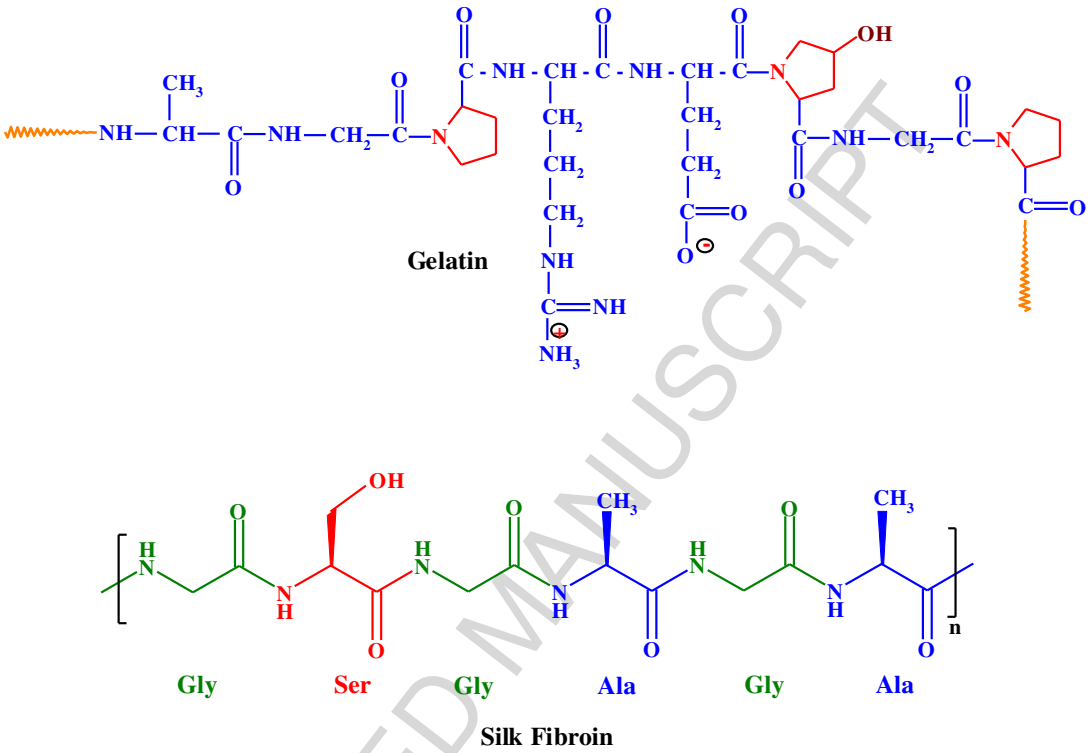
3. Natural polymers

Natural polymers are generally produced by microorganisms, plants, and animals [23-25]. These polymers are categorized into three main classes including, polypeptides, polysaccharides, and polyesters [12, 24]. Early interests regarding the natural polymers are their hopeful biomedical applications in cosmetics and pharmaceutical industries as well as regenerative medicine. Some exclusive characteristics of natural polymers for biomedical applications are their extraordinarily elevated stability, variable/controllable solubility, superior structural design, 3D geometry, low immunogenicity, excellent biocompatibility and cytocompatibility, antigenicity, and often specific tissue/cell targeting [26, 27]. It is well documented that in comparison with semi-synthetic or synthetic polymers, natural polymers have better performance in mimicking the ECM and interaction with tissues, mainly due to the high similarity with tissue surroundings [28]. The chemical structures of the most important members of natural polymers that applied as scaffolding materials in TE are shown in Schemes **1** and **2**. Despite the above mentioned advantages and wide applicability of natural polymers, there are several drawbacks such as high production cost in some cases (*e.g.,* collagen and hyaluronic acid), batch to batch variation mainly due to the complexity of their structure and chemical composition, complex macromolecular architecture and morphology, uncontrolled rate of hydration, resources limitation, and possibility of microbial spoilage which may restrict their applications in TE [29]. In some cases, natural polymers suffer from poor processability (*e.g.,* cellulose and chitosan), and low mechanical properties (*e.g.,* polypeptides). Furthermore, degradation and catabolization

rate of some naturally fabricated scaffold is higher in comparison with the regeneration rate of the host tissue in large part due to their low stability. Considering these thematic issues, manipulating of the architecture and functionality of the natural polymers could open new opportunities toward biomaterials with appropriate degradation, mechanical, structural and composition properties that qualify them for various successful TE [30]. In this context, some strategies such as chemical modification of natural polymers [22], preparation of polymeric blends using synthetic or semi-synthetic polymers [31], crosslinking [32], and physical modification [33] have been proposed to solve above mentioned problems. These strategies will be discussed in the following sections.



Scheme 1. The important members of polysaccharides have been applied as scaffolding materials.



Scheme 2. The chemical structures of gelatin and silk fibroin as scaffolding polypeptides.

3.1. Chemical modification of natural polymers

Chemical modification of natural polymers can be considered as an efficient and powerful tool toward improving the physicochemical, mechanical as well as biological characteristics of these polymers [34, 35]. In general, chemical modification is carried out through the functionalities (*e.g.,* amine and hydroxyl groups) at the polymer backbone. This type of modification can be achieved through various approaches including, polymer grafting [36], small molecules attaching [37], as well as some chemical reactions such as esterification, etherification, silylation, quaternization, acetylation, oxidation, and alkylation [38]. Among the above-mentioned

approaches, the polymer grafting strategy with tailored surface properties is the most attractive option, mainly due to inherent physicochemical as well as biological characteristics of the resultant copolymer [39]. This process in large part applied in the case of cellulose [40], chitosan [41, 42], gelatin [43], and collagen [44] toward the synthesis of more appropriate biomaterials for scaffolding. In general, three grafting methods including, "grafting from", "grafting to" and "grafting through" have been proposed for the synthesis of natural polymers-based copolymers. Among these, the "grafting from" is the most commonly used approach toward the synthesis of natural polymers-based copolymers using a macroinitiator [45]. In this context, the "grafting from" approach using reversible-deactivation radical polymerization (RDRP) is great of interest. This polymerization technique is divided into three main categories including:

a) Nitroxide-mediated radical polymerization (NMRP) [46-48]

b) Reversible addition of fragmentation chain transfer (RAFT) polymerization [49-51]

c) Atom transfer radical polymerization (ATRP) [52-54].

These polymerization approaches have been developed toward the synthesis of copolymers with controlled molecular weight, narrow dispersity, and complex macromolecular architectures. Among these, ATRP and RAFT are the most popular, and NMRP is the least employed approach toward the synthesis of natural polymers-based copolymers [45].

As mentioned, the surface properties of natural polymers can be engineered through the synthesis of copolymers. For instance, grafting of poly(lactic-*co*-glycolic acid) (PLGA) onto chitosan improves its mucoadhesive potential [55, 56]. The PEGylation of chitosan have been affects the mucoadhesive potential of chitosan, too [57]. It is well documented that the PEGylation improves the toxicity profile of natural polymers, while affects the epithelial tight junctions and increases permeability [58-60]. The PEGylating of cellulose improves its tensile strength and

biocompatibility during TE [61]. Some other fabricated biomaterials through the grafting of synthetic polymers onto naturally occurring macromolecules are listed in Table **1**.

Table 1. Some examples of biomaterials fabricated through the grafting of synthetic polymers onto naturally occurring macromolecules.

Composition	Target TE	Fabrication method	Form of scaffold	In vitro main findings	References
PLGA-collagen	Ligament	Forming collagen microsponges in the openings of a PLGA-knitted mesh	Sponge-like	Causes ligament regeneration	[62]
Alginate/gelatin modified PLGA	-	Surface entrapment and entrapment-graft	Electrospun nanofiber	Exhibits better biocompatibility	[63]
Gelatin/*N*-maleic acyl-chitosan grafted PLA	Vascular grafting	Photoinitiation	Microstructures with a smooth surface	Enhances HUVEC spreading and flattening	[64]
Chitosan/PLGA	-	Chitosan grafted onto surface of PLGA	Electrospun nanofiber	-	[56]
Gelatin-modified sodium alginate/gelatin-modified PLGA	-	Surface entrapment and entrapment-graft	Electrospun nanofiber	-	[63]
Hyaluronic acid/PHEMA	Lung TE	Grafting	Copolymer film	Supports alveolar cell adhesion and growth	[65]
PCL-*graft*-collagen	-	Polyesterification	-	Enhances spindle-like morphology, spreading homogeneously of fibroblasts	[66]
PCL-*graft*-collagen	Tendon TE	Polyesterification	Spongy films	Supports cell adhesion and proliferation	[67]

PLA: poly(*D*, *L*-lactide), HUVEC: human umbilical vein endothelial cell, PHEMA: poly(2-hydroxyethyl methacrylate), PCL: poly(ε-caprolactone)

3.2. Natural polymers-based blends

3.2.1. Combination of two or more natural polymers

Polymer blends refer to a polymeric martial composed of at least two polymers, which resulted to enhanced physicochemical features compared than those of distinct polymer [68]. In a blend, each polymer holds its specific physicochemical and biological properties. These materials possess enhanced strength and stiffness while show low density and loosed weight compared with those of polymer used alone [22]. However, the main drawback of bulk natural polymer, which demands development of blends is their low mechanical performance and high sensitivity to an environmental condition such as humidity and temperature [22].

In general, polymer blends are categorized into two classes as either miscible or immiscible blends, depending on the interactional behavior of the polymers that constitute the blend. Miscible blends have similar properties that are comparable to random copolymers or homopolymers. In contrast, immiscible blends have multiple glass transition temperatures (T_g) owing to the distinct separation between the constituent polymers [69]. To solve this problem in immiscible blends, the use of compatibilizer can be considered as an effective strategy due to reducing interfacial tension and subsequently increasing the interactional forces between the constituent polymers [70].

Some strategies including, physical blending (*e.g.,* melt or solvent processing), freeze drying, and electrospinning can be employed for the preparation of natural polymers-based blends [20]. However, melt processing is not suitable approach in the case of some natural polymers (especially proteins), because the high temperature can lead to denaturation and degradation of such biopolymers [71]. Among these, co-electrospinning of natural polymers to afford nanofibrous scaffolds is particular of interest, mainly due to inherent characteristics of the final scaffold as listed at the following:

a) Similar morphology to the human native ECM

b) Porous network with the high surface area and interconnectivity

c) Ultra-thin continuous fibers (ranging from 5 to 500 nm)

d) The adjustable pore size distribution

e) Simplicity, scalability, and more cost-effectivity

f) Applicability for both organic and inorganic materials [72].

According to the mentioned features, these types of scaffolds meet the most requirements toward a successful TE.

Numerous blends through the combination of two or more natural polymers have been developed and used for scaffolding due to their appropriate physicochemical as well as biological features. For example, Lin et al. fabricated a blend of keratin/chitosan (CS) which holds the bioactivity advantages of keratin and enhanced physiochemical characteristics of CS for TE [73]. Studies showed that the thermal stability, physical features and cross-linked properties of the sponge deduced from a blend of silk fibroin/CS polymers are better than that for sponge made of pure silk fibroin or pure CS [74].

It is well documented that in bone TE, a blend of gelatin and collagen play an important role to accelerate the formation of apatite layer on the bio-blend films indicating their role as apatite nucleation inducer [75]. In addition, in bone TE, a poor interaction exists between hydroxyapatite (HA) and CS phases so that the HA/CS blend scaffold has poor physicochemical properties. In this context, a blend of CS and carboxymethyl cellulose (CMC) could be a good solution for the issue during bone TE. CMC is a natural biodegradable and biocompatible anionic polymer and is very similar to CS in structure, thus, there is strong ionic crosslinking action between CMC, CS and thus HA [76]. Fibronectin, a polypeptide, can promote cell

adhesion, and CS is known for its ability to promote differentiation of stem cells to several lineages. Therefore, the combination of mentioned natural polymers leds to more effective scaffolding biomaterial [77, 78].

In conclusion, the blending of two or more naturally occurring polymers is an efficient and versatile strategy for production of biomaterials with synergic physicochemical as well as biological features that qualified them toward a successful TE. Some examples of biomaterials fabricated through the combination of two or more natural polymers for scaffolding is summarized in Table **2**.

Table 2. Some examples of biomaterials fabricated through the combination of two or more natural polymers for scaffolding.

Composition	**Target TE**	**Fabrication method**	**Form of scaffold**	**In vitro main findings**	**References**
Cellulose/gelatin scaffold loaded with VEGF-silk fibroin nanoparticles	Skin TE	Lyophilizing	The porous composite containing VEGF-nanoparticles with an average pore size of 171 ± 71 μm	Improves cell proliferation and viability *in vitro* and promotes vessel blood formation *in vivo*	[79]
CMC/silk fibroin	Bone TE	Free liquid surface electrospinning	Electrospun nanofiber	Improves osteoblastic differentiation hMSCs	[80]
Gelatin/carboxymethyl chitosan/nano-HA	Bone TE	High stirring induced foaming of composite followed by freeze drying	Macroporous composite	Increases the viability, proliferation, and differentiation as well as induces mineralization of differentiated HwjhMSC-MT	[81]
Gabapentin-loaded cellulose acetate/gelatin	Neural TE	Wet-electrospinning	Electrospun nanofiber	Enhances the regeneration of sciatic nerve defect *in vivo*	[82]
Gelatin/bacterial cellulose	-	Freeze-drying and thermal cross-linking	Spongy	Enhances Vero cell proliferation	[83]
Silk fibroin/ CS/gelatin	Bone TE	Chemical cross-linking and freeze-	Spongy	Enhances MC3T3-E1 cells biocompatibility	[84]

		drying		and induces osteogenesis	
Silk fibroin/gelatin	Cartilage regeneration	Gelation and 3D printing	Square Prism	Shows superior performance for cartilage repair in a knee joint	[85]
Silk fibroin/gelatin	Small diameter blood vessel regeneration	Crosslinking using a Michael-type addition reaction followed by electrospinning	Electrospun nanofiber	Improves viability and spread morphology of L929 fibroblasts	[86]
Silk fibroin/collagen	-	Blending	Cell encapsulated hydrogels	Provides a biocompatible matrix for cell proliferation and differentiation	[87]

(hMSCs): Human mesenchymal stem cells, HwjhMSC-MT: Human Wharton's jelly MSC micro-tissue

3.2.2. Combination of natural and synthetic polymers

In comparison with natural polymers, synthetic polymers have good mechanical properties and thermal stability. However, the most important concern regarding the synthetic polymers is their biological aspects (*e.g.,* biocompatibility and biodegradability) [10]. According to these facts, the blending of natural and synthetic polymers can produce a new class of biomaterials due to specific properties of both polymer types. These blends have been called bio-artificial or bio-synthetic polymeric materials [10].

So, some types of biocompatible synthetic polymers such as poly(vinyl alcohol) (PVA) and thermoplastic polyurethane (TPU) may enhance the mechanical properties of obtained blends, which candidate them for a successful TE [88]. Poly(ε-caprolactone) (PCL), an aliphatic and synthetic biodegradable polyester, is commonly used polymer in combination with different natural polymers such as starch, gelatin, collagen and CS in TE, mainly due to its superior mechanical properties and tailorable degradation kinetics [89-93]. However, observations

revealed its limited cell affinity, adverse foreign body response *in vivo*, and lack of surface cell recognition sites [94]. On the other hand, gelatin is a natural polymer which widely used in different aspects of TE. The hydrophilic gelatin shows biological recognition, low immunogenicity, and antigenicity. However, the main drawbacks are weak mechanical strength and rapid degradability. Obviously, the combination of gelatin and PCL is an efficient attitude to overcome shortcomings of each polymer in TE [95]. Well as, the collagen and elastin (the primary structural components of the ECM in vascular tissues) have been used for fabrication of scaffolds toward vascular grafting [96, 97]. Although the resulted scaffolds enhance the cell adhesion, proliferation and successful cell migration, however, fail to achieve desired mechanical features, integrated and swelled structure. Some evidences showed that the blending of collagen with PCL or poly(L-lactide-*co*-ε-caprolactone) (PLCL) enhances the physical characteristics of resulted scaffold in comparison with neat collagen [98]. Moreover, blending of CS with PCL combines the biological affinity of the CS (*e.g.,* facilitation of cell adhesion and proliferation, providing hydrophilicity and cell recognition sites, and also the establishment of a porous structure) and physicochemical features of PCL (*e.g.,* enhancing the mechanical properties) [99]. PVA is another important synthetic polymer that used in scaffolding to prepare polymer-bioglass sol colloid system. Some studies reported its biocompatibility and wide usage in the successful development of controlled delivery systems and TE [100-102]. However, various investigations suggested that the PVA possess limited ability to integrate into the living tissue [103]. Silk fibroin (SF) has been used extensively in combination with PVA and other synthetic polymers for development of scaffolds in large part due to its superior biocompatibility, tunable mechanical property, biodegradability, less inflammatory property, and enhancement of biological properties of PVA [104-106].

PLGA is an FDA approved synthetic polymer that widely used as scaffolding material, mainly due to the acceptable mechanical properties, good biocompatibility, amendable biodegradability, and generating biocompatible products resulted from physical degradation and biological catabolism [107, 108]. However, its polyester surface is hydrophilic, and lack of functional group that limits its interactions with cell surfaces and decreases its tunability as scaffolding materials in fruitful TE [16, 109, 110]. These thematic issues can be solved through its blending with natural polymers (*e.g.,* collagen and gelatin) using electrospinning process. The resultant biomaterials enhance the surface roughness, hydrophilicity and cell adhesion tendency [16]. Table **3** summarizes some examples of biomaterials fabricated through the combination of natural and synthetic polymers for scaffolding.

Table 3. Some examples of biomaterials fabricated through the combination of natural and synthetic polymers for scaffolding.

Composition	Target TE	Fabrication method	Form of scaffold	In vitro main findings	References
PCL/silk fibroin	Bone TE	Electrospinning	Electrospun nanofiber	Has acceptable biocompatibility	[111]
Spider silk protein/PCL/gelatin	Small caliber vascular TE	Electrospinning	Electrospun nanofiber	Exhibits better blood and tissue compatibility	[19]
PCL/antheraea pernyi silk	Oriented tissues TE	Electrospinning	Electrospun nanofiber	Support PC12 neuron-like cell growth and guide neurite outgrowth	[18]
PCL or P3Hb nanofibers combined with silk	Ligament TE	Electrospinning	Electrospun nanofiber	Enhanced cytocompatibility	[112]
PCL/silk fibroin/collagen	Urethral TE	Electrospinning	Electrospun nanofiber	Enhanced cytocompatibility	[17]
PCL/gelatin	-	Electrospinning	Electrospun nanofiber	Enhances mesenchymal stem cell attachment, spreading, and	[113]

				cytoskeleton organization	
PCL/gelatin	Vascular TE	Electrospinning and photocrosslinking under UV	Electrospun nanofiber	-	[114]
PLGA/gelatin	Neural TE	Freeze casting and freeze drying	A unidirectional microstructure with a number of random pores	Improves P19 cell differentiation	[115]
PLGA/collagen	Skin TE	Coating, and electrospinning	Electrospun nanofiber	Enhanced cytocompatibility	[16]
Collagen/PLA, CS/PLA, and collagen/CS/PLA	Cartilage TE	Combining of freeze-dried natural components and synthetic PLA mesh	Spongy/ nanofiber	Enhanced cytocompatibility and cell penetration capability	[116]

3.2.3. Mineralization

During the bone remodeling, there are clear evidences that created osteoblasts secret osteoid in the site of bone regeneration, which is eventually mineralized into new bone. It seems that many factors such as osteoclast and osteoblast products, the extracellular levels of Pi and PPi, hormones, circulating factors in the site of bone remodeling can expose remarkable effects on the bone regeneration. Therefore, it looks that the mineralizing polymer surfaces by the incorporation of inorganic materials such as hydroxyapatite (HA), bio-silica, metalloenzymes (*e.g.,* alkaline phosphatase; ALP), and bioactive glasses is an effective approach for improving the mechanical as well as biological (*e.g.,* protein adsorption and subsequent cell adhesion) features of the final scaffold in hard TE (Figure **1**). In addition, this approach may be lead to the sustained release of growth factors and genes [117-119]. Among these, calcium phosphates (CaPs) are particular of interest due to their abilities to mimic the inorganic components of hard tissues. In addition, CaPs have some other superior properties including, porosity, small particle size, and chemical composition or mineral frame [120]. However, CaPs have some problems such as poor mechanical strength and low macroporosity. This problem can be solved by the reinforcing of CaPs using biodegradable natural or synthetic polymers that lead to composites

containing continuous CaP with a dispersed polymer component [119]. For example, mineralization of collagen using CaP is an efficient approach for modification of physicochemical as well as biological features of this natural macromolecule [121, 122].

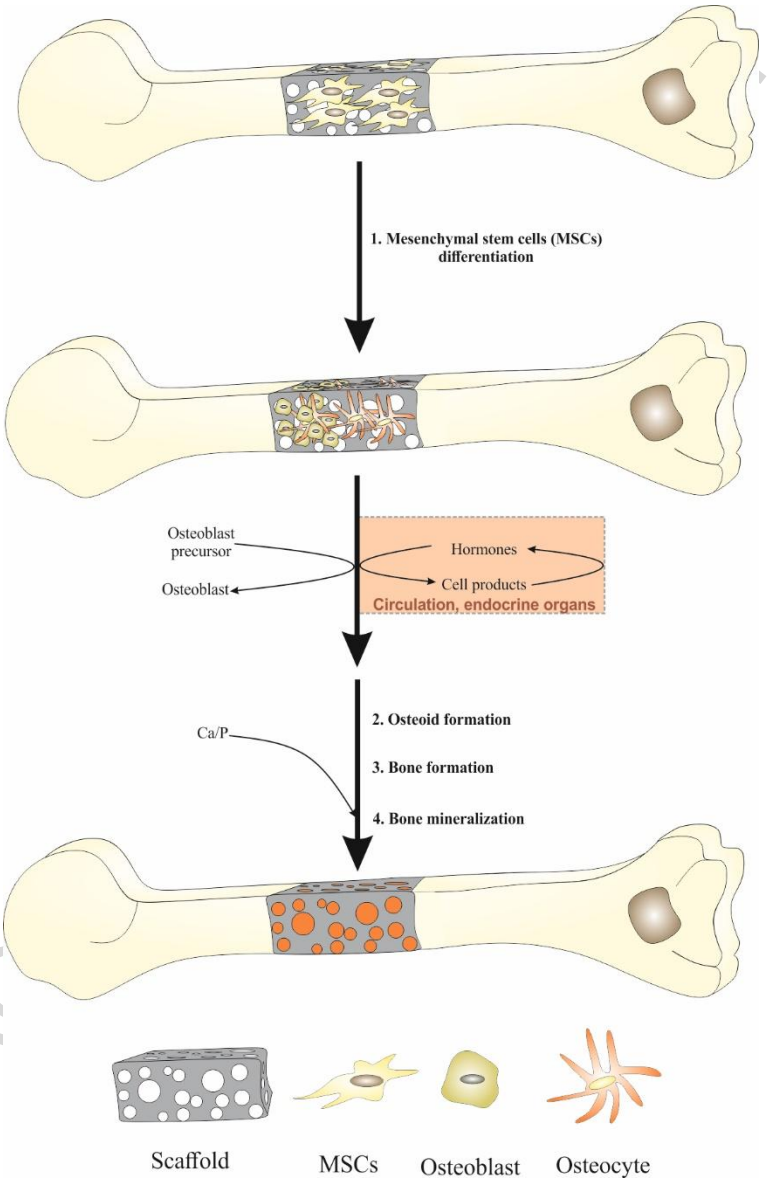


Figure 1. The schematic representation of bone TE and different parameters which influence the process.

This strategy has attracted tremendous interest in bone or dental TE due to promote bioactivity (*i.e.,* the formation of a chemical bond with surrounding bone tissue after implantation), promotion of osteoblastic differentiation through increased stiffness, and enhanced binding of growth factors that stimulate bone healing [123-125]. Dhand and colleagues [126] reported the bio-inspired fabrication of bone-like composite structures by electrospinning of collagen containing catecholamines and Ca^{2+}. This strategy enhances mechanical properties of collagen. In addition, it was found that human fetal osteoblasts seeded on the fabricated scaffolds display enhanced cell adhesion, proliferation, penetration, differentiation and osteogenic expression of osteocalcin, osteopontin and bone matrix protein when compared to pristine collagen or tissue culture plates. Table **4** summarizes some examples of mineralized natural polymers for scaffolding in hard TE.

Table 4. Some examples of mineralized natural polymers for scaffolding in hard TE.

Composition	**Fabrication method**	**Form of scaffold**	**In vitro main findings**	**References**
Gelatin/carboxymethyl chitosan/nano-HA	High stirring induced foaming of scaffold followed by freeze drying	3D macroporous scaffold	Increases the percentage of viability, proliferation, and differentiation as well as higher mineralization of differentiated human Wharton's jelly MSC microtissue (wjhMSC-MT)	[81]
Gelatin/HA	Crosslinking and electrospinning	Electrospun nanofiber	Enhances cell proliferation	[127]
Collagen-coated PLGA-HA	Combination of blending and coating strategies	Porous microparticles	Promotes the repair of skull defect	[128]
Insulin-loaded nano-	Blending	Spongy and	Possesses	[129]

HA/collagen/PLGA composite		microspores scaffold	favorable biological function for bone marrow mesenchymal stem cells adhesion and proliferation, as well as the differentiation into osteoblasts	
CS/nano-HA/nano-zirconium dioxide	Freeze-drying	Scaffold with interconnected pores (spongy)	Promotes osteoblast differentiation	[130]
CS/HA containing simvastatin (SIM)-loaded PLGA microspheres	The freeze-drying technique with a modified water-oil-water emulsion	Interconnected microporous scaffold	Promotes cell proliferation and induces osteogenic differentiation	[131]
Silk fibroin/CS/nano-HA	Crosslinking/freeze drying	Scaffold with interconnected pores (spongy)	Enhances rabbit radial bone defect	[132]
Alginate/hydroxyethyl cellulose/HA	Lyophilization	Scaffold with interconnected pores (spongy)	Increases human mesenchymal stem cells population	[133]
Cellulose/nano-HA	Electrospinning	Electrospun nanofiber	Enhanced cytocompatibility	[134]
Cellulose nanocrystals reinforced xanthan gum (XG)/silica glass (SG)	Freeze drying	Highly porous scaffold	Enhanced cytocompatibility	[135]
PVA and collagen incorporated with zeolite and silica NPs	Electrospinning	Electrospun nanofiber	Enhances chondrocyte cell proliferation	[136]
Silica-hybridized collagen	The sol-gel process	Hydrogel	Enhanced cell proliferation and possesses promoted cell adherence properties	[137]
Silica/apatite co-mineralized collagen	Surface coating through incubation and solvent processing	Cross-linked microparticles	Inhibits differentiation of RAW 264.7 cells into	[138]

			multinucleated osteoclasts and reduces the osteoclast function	
Calcium phosphate/bioactive glass composite chitosan/collagen	Immersing the inorganic phases of three different calcium phosphate mixing bioactive glass (BG) with PCL as a binder in an organic phase of chitosan/collagen matrix and final freeze drying	Porous scaffold	Promotes osteoblast attachment and proliferation	[139]
Gelatin/chitosan/bioactive glass	Blending/immersing the inorganic phase I organic phase and final freeze drying	Spongy	Enhances angiogenesis and cell growth	[140]

3.3. Crosslinking strategy

In the case of some natural polymers, especially polypeptides, crosslinking strategy is the first choice toward the modified corresponding polymer [141, 142]. Crosslinking is a process that connects the functional groups of a polymer chain to another one through covalent bonding or supramolecular interactions (*e.g.,* hydrogen bonding and ionic interactions). The intense interest in the application of this strategy is originated from its simplicity, effectiveness, and cost benefits. Crosslinking leads to some satisfactory improvements in mechanical properties and aqueous stability [32, 143]. However, degradability and accessibility to functional groups and their degradation rate may be decreased in the cross-linked polymers. In addition, changes in functionality and rheology, as well as increase cytotoxicity are the other disadvantages of this strategy [143].

In general, crosslinking techniques can be divided into three main categories including, chemical, physicals, and enzymatic approaches [144, 145]. In the chemical crosslinking, polymeric chains are attached together by covalent bonds. These type of materials are stable and cannot be dissolved in any solvents [146]. Chemical crosslinking may be achieved using both small molecules (*e.g.,* glutaraldehyde) and macromolecules (*e.g.,* poly(carboxylic acids)). Glutaraldehyde is the most widely used agent for crosslinking of natural polymers mainly due to its inherent characteristics including, reaction with various functional groups (*e.g.,* amine and hydroxyl), and capable to provide materials with substantial improvement in mechanical properties [145, 147, 148]. However, the glutaraldehyde-crosslinked materials showed cytotoxicity in some cases [149]. According to this, green chemicals and more efficient crosslinking approaches are necessary to obtain biomaterials with proper physicochemical as well as biological features for biomedical applications. Some of the undesirable outcomes of chemical crosslinking can be solved through the physical approaches. Various approaches such as ionic and hydrogen interactions may be used toward physical crosslinking of natural polymers. For example, collagen can be cross-linked by a combination of glucose and UV irradiation through the UV-generated free radicals. This approach improves the mechanical properties and decreases enzymatic degradation of collagen [150]. Another most important case of physical crosslinking is the crosslinking of alginate using divalent cations such as calcium (Ca^{2+}). In addition, blending of starch/CMC [151], gelatin/agar [152], and hyaluronic acid/methylcellulose [153] form physically cross-linked and injectable gel-like structures.

Enzyme-catalyzed crosslinking is a relatively new and efficient approach that attracted more attention due to its superior features including, excellent crosslinking efficiency, short reaction time, mild reaction conditions and high biocompatibility. This approach is suitable for *in-situ*

gelation systems [154]. More recently, transglutaminases (TGase; protein glutamine gamma-glutamyltransferase) [155], and horseradish peroxidase (HRP)/hydrogen peroxide (H_2O_2) [156] have been used as enzymatic agents for fabrication of different types of scaffolds. Some other examples of cross-linked natural polymers for scaffolding are listed in Table **5**.

Table 5. Some examples of cross-linked natural polymers for scaffolding.

Composition	Target TE	Fabrication method	Form of scaffold	In vitro main findings	References
Collagen	Tendon TE	Lysyl oxidase-mediated collagen crosslinking	Spongy	-	[157]
Collagen/glycosaminoglycan (GAG)	Bone TE	Dehydrothermal (DHT) crosslinking	Spongy	Enhances cell number and cell metabolic activity	[158]
Gelatin/HA	Bone TE	Co-precipitation of hydroxyapatite within gelatin solution followed by freeze-drying	Spongy	Enhances cell attachments and proliferation	[159]
Bovine HA/ gelatin/CS	Bone TE	Crosslinking by glutaraldehyde	Microporous spongy	Possess good cell adhesion behavior	[160]
CS/gelatin	Liver TE	Crosslinking by natural genipin	Microporous spongy	Enhances cell proliferation and tissue penetration	[161]
CS	Cartilage TE	Hydrothermal crosslinking (autoclaving)	Interconnected and microporous scaffold	Improves cell adhesion and proliferation	[162]
Silk fibroin microfibers and CS modified poly (glycerol sebacate)	Skin TE	Particulate leaching and freeze-drying	Interconnected and open porous scaffold	Enhances cells attachment, proliferation, and deep penetration into artificial tissue	[163]

3.4. Physical modification

The physical modification is an efficient and safe approach for improvement of physicochemical as well as biological features of natural polymers. This modification technique is simple, cheap, and safe because requires no chemicals or biological agents. Various approaches including hydrothermal, corona electrical discharges, radiation technique (*e.g.,* UV, gamma-ray, and laser irradiation), pressure, shear, steam treatment, plasma treatment, electron beam treatments, and flame treatment may be applied for physical modification depending on the type of natural polymer [164]. This modification approach is extensively applied to starch [165] and cellulose [166] as the most abundant organic compounds in nature.

4. Synthetic polymers

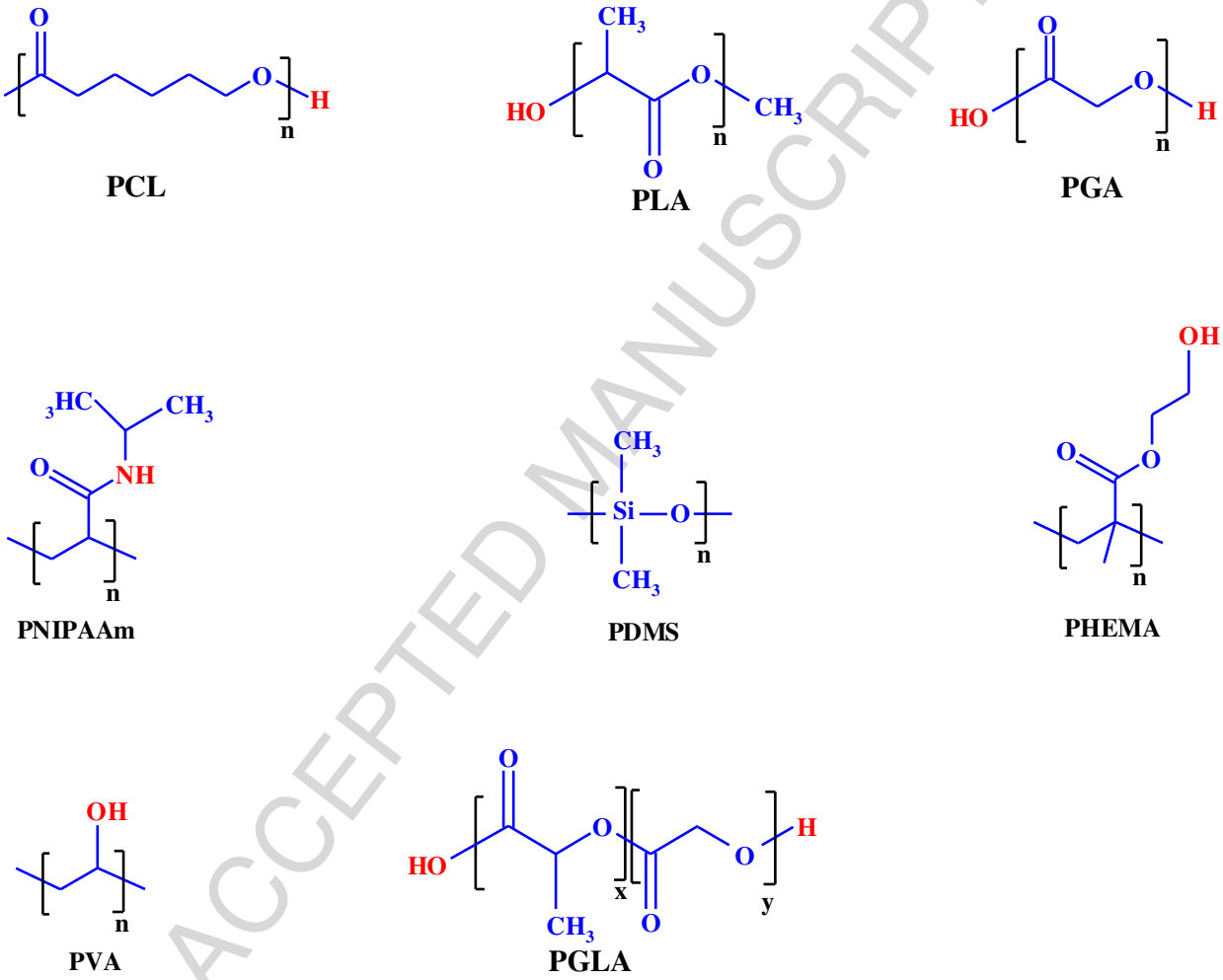
Synthetic polymers can be easily produced on a large scale and low cost with controlled molecular weight and functionality. However, the main drawback of synthetic polymers in the field of biomedical applications (*e.g.,* regenerative medicine) is the lack of biological cues such as cell recognition signals (known as biocompatibility) as well as biodegradability in most cases. Some synthetic polymers such as PCL [167, 168], poly(glycolic acid) (PGA) [169], PLA [170], PLGA [108], PVA [171], PHEMA [172], poly(dimethylsiloxane) (PDMS) [173], and poly(*N*-isopropylacrylamide) (PNIPAAm) [174] have been extensively applied as scaffolding material. The chemical structures of these polymers are shown in Scheme **3**.

The most important advantages of these polymers are divided into two properties as follows:

1) The structure and chemical composition of these polymers can be easily tailored to afford desired physicochemical features that qualified them for successful TE.

2) These synthetic polymers are generally subjected to biodegradation because of the susceptibility of their aliphatic ester linkage to hydrolysis or via activities of esterase enzymes secreted by cells [11].

Despite above advantages, as mentioned earlier, the most important drawback of these polymers is biocompatibility. Considering this fact, these polymers should be modified before their application as biomaterials for scaffolding. Some modification approaches are discussed in the following.



Scheme 3. The chemical structure of some synthetic polymers that applied for scaffolding.

4.1. Chemical modification

In general, the developed approaches for surface modification of synthetic polymers improve their hydrophilicity, biocompatibility, vascularization and surface density of functional groups in order to immobilization of biomolecules for TE [175-177]. The first option for this purpose is engineering the functionality of these polymers through the attaching of small- or macro-molecules [178]. This strategy improves the hydrophilicity and surface charge of the biomaterial and leads to favorable cell adhesion [179, 180].

In this context, aliphatic polyesters such as PLA, PLGA, PCL, and PGA are the most important categories of synthetic polymers for scaffolding. These polyesters are synthesized through ring-opening polymerization (ROP) of the corresponding monomer [181, 182]. In addition, some polyesters such as poly(butylene succinate) (PBS) can be produced by polycondensation of diacid and diols. In comparison with ROP approach, polycondensation does not require strict reaction conditions and has been utilized for industrial mass production [183].

However, slow degradation rate, lack of natural recognition sites, and hydrophobicity are the most important disadvantages of these polymers [184]. Therefore, modification of these polymers is pivotal for TE applications in order to ideally adjust cell/tissue biological functions. In this context, two main approaches including, pre-functionalization and post-functionalization approaches have been introduced toward modified polyesters. These approaches have been extensively reviewed elsewhere [183, 185]. Due to the importance and extensively usage of aliphatic polyesters as scaffolding biomaterials, some features of PLA and PCL are discussed in the following.

PCL is a biodegradable aliphatic linear polyester with semi-crystalline properties that gain the approval of FDA. The most important advantages of PCL are hydrolytic degradation through the cleavage of the ester linkages and formation of monomeric caproic acid, biodegradability,

biocompatibility, and bio-resorbability [186]. However, the biomedical applications of PCL might be limited mainly due to its high crystallinity and slow degradation rate [187]. An efficient and versatile approach to overcome these defects is its chemical modification using various approaches. In this respect, the most important plausible chemical strategies to upgrade the properties of PCL are hydrolysis using sodium hydroxide (NaOH) [188], aminolysis [188, 189], as well as polymer grafting [190, 191].

PLA is another synthetic thermoplastic polyester that extensively used for biomedical applications. PLA has some superior physicochemical as well as biological features as follows:

a) Excellent biocompatibility and biodegradability

b) Eco-friendly property (derived from renewable resources such as corn, wheat, or rice)

c) Excellent thermal processability in comparison with other synthetic polymers (*e.g.,* PEG and PCL)

d) Less production energy than those of the petroleum-based polymers (approximately 25–55%) [192-194].

However, poor toughness, lack of natural recognition sites, slow degradation rate, and hydrophobicity are the most important disadvantages of PLA. In this context, copolymerization of lactic acid with other monomers through polycondensation or ring-opening copolymerization is the most important chemical modification approach [192]. Another efficient strategy is the synthesis of PEG and PLA copolymer (PLE). These copolymers can be synthesized through both ring-opening polymerization of lactide using PEG as macroinitiator or polyesterification approaches [195, 196]. Copolymerization of PEG with lactide can modulate the biodegradation rate, the hydrophilicity, as well as mechanical properties in comparison with PLA homopolymer

[196]. At the end of this section, some examples of chemically modified synthetic polymers for scaffolding is summarized in Table **6**.

Table 6. Some examples of chemically modified synthetic polymers for scaffolding.

Composition	Target TE	Modification Approach	Form of scaffold	In vitro main findings	References
PCL	-	Surface modified *via* aminolysis	Film scaffold	Improves the cell attachment and proliferation	[197]
PCL	Peripheral nerve TE	Surface modified *via* hydrolysis and aminolysis	Film scaffold	Enhances cell proliferation	[188]
PVA	-	Surface modified using cell-adhesive peptide RGDS	Hydrogels	Support the attachment and spreading of fibroblasts	[198]
PCL	-	Gamma irradiation-induced grafting of acrylic acid	Film scaffold	-	[199]
PLA	Neural TE	Surface modified by epidermal growth factor	Electrospun nanofiber	Improves cell proliferation in the absence of growth factor	[200]
PLGA	-	Surface modified *via* hydrolysis and aminolysis	Film scaffold	-	[201]
PDMS	-	Fibronectin and collagen type 1 were grafted on the scaffold surface by (3-aminopropyl)triethoxy silane (APTES) and crosslinking using glutaraldehyde (GA)	Film scaffold	Enhances the adhesion and proliferation of mesenchymal stem cells	[202]
Hyperbranched aliphatic	-	Grafting of polythiophene (PTh)	Electrospun nanofiber	Improves the cell attachment and	[203]

polyester (HAP)		onto HAP and blending with PCL		proliferation	
PEG	Bone TE	Grafting of PTh onto PEG and blending with PCL	Electrospun nanofiber	Improves the cell attachment and proliferation	[204]
PVA	-	Oxidized	Hydrogel	Don't elicit severe inflammatory reactions in vivo	[205]
Polyurethane (PU)	-	Modified by acrylamide using plasma radiation	Film scaffold	Improves the cell proliferation	[206]

4.2. Surface engineering using physical approaches

The surface characteristics of biomaterials including, stiffness, roughness, and topography that influence the cell adhesion and proliferation can be easily manipulated in synthetic polymers [207, 208]. In general, physical approaches introduce oxygen-containing functional groups onto polymer surfaces, in order to improve adhesion and wettability that have important roles in TE. The most important physical approaches include radiation-induced surface modification (UV, gamma-ray, and laser irradiation) [209], ion beam based processes [210], vapor based coatings [211], plasma-assisted coating methods [212], electron beam treatments [213], flame treatment [214], and corona discharge treatments [215]. These approaches have some advantages over chemical modification as follows:

a) A mild condition in most cases

b) More environmental friendly due to the lack of any chemical agent

c) No undesirable changes in the polymer surface morphology

d) Simplicity, scalability, and more cost-effectivity (in most cases)

e) Applicability to a huge range of synthetic polymers [209, 216].

Some examples of physically modified synthetic polymers for scaffolding is summarized in Table **7**.

Table 7. Some examples of physically modified synthetic polymers for scaffolding.

Composition	Target TE	Modification Approach	Form of scaffold	In vitro main findings	References
PCL	-	Laser surface modification	Film scaffold	-	[217]
PCL	Bone TE	Plasma Modification	Spongy and porous scaffolds	Increases of cell viability	[218]
PLGA	Soft TE	Electron beam irradiation	Electrospun nanofiber	Cell proliferation behavior on all electron beam irradiated PLGA mats was similar to the control PLGA mats	[219]
PCL	Bone TE	Physical incorporation of ginseng extract into PCL electrospun nanofibers	Electrospun nanofiber	Higher calcium content, alkaline phosphatase activity and higher mineralization of mesenchymal stem cells were observed	[220]
PLGA	-	Plasma modification	Electrospun nanofiber	Enhances mouse fibroblasts cells adhesion and proliferation	[221]
Polyurethane	Cardiac TE	Plasma mediated protein immobilization	Film scaffold	Enhances cell proliferation and attachments in vitro, and implants in rat aortic interposition model in vivo	[222]
PCL	-	Plasma mediated laminin protein immobilization	Electrospun nanofiber	Enhances cell adherence	[223]
Polyurethane	-	Acrylamide modification using plasma radiation	Film scaffold	Enhances cell proliferation and adherence	[206]
PLA	-	Plasma modification	Electrospun nanofiber	-	[224]

4.3. Biological modification

Despite the FDA approval support of some synthetic polymers (*e.g.,* PCL, PLA, and PLGA), safety concerns regarding the use of these polymers are still remain, however, because foreign materials are inherently thrombogenic. The main reason for this is denaturation of proteins, activation of coagulation factors, propagation of thrombi, provocation of inflammatory responses, and accumulation of debris [225-227]. Biological modification of these polymers is an efficient approach for biomedical application due to enhancing the compatibility and possibility of interaction with complex biological environments. In this context, the most common approaches are a surface coating, entrapment, self-assembly, and chemical grafting [228].

An efficient approach is bio-functionalization, in which the ECM peptide sequences promote cell behavior in a manner similar to fibronectin sequences (REDV, PHSRN, RGD, and GRGDSP), laminin-derived recognition motifs (IKLLI, IKVAV, LRE, PDSGR, RGD, YIGSR), and collagen type I-derived sequences (DGEA, Tenascin-C-derived peptides D5 and D50) [229]. These peptide ligands directly interact with cell surface receptors and improve the cell adhesion and differentiation processes. For example, an efficient approach for the biological modification of PLA is the synthesis of poly(lactic acid-*co*-lysine) copolymer followed by attaching a peptide containing an RGD sequence that led to enhanced cell adhesion [185]. This type of modification has been recently summarized by Balaji and co-workers [230]. Table **8** summarized some examples of scaffolds that fabricated by biologically modified synthetic polymers.

Table 8. Some examples of biologically modified synthetic polymers for scaffolding.

Composition	Target TE	Modification agent	Form of scaffold	In vitro main findings	References
PLGA	-	Modified by poly(l-lysine)	Microporous scaffold	Enhances cell adherence and proliferation	[231]

PDMS	-	Fibronectin and collagen type 1were grafted on the scaffold surface by (3-aminopropyl)triethoxy silane (APTES) and cross-linker glutaraldehyde (GA) chemistry	Film scaffold	Enhances the adhesion and proliferation of mesenchymal stem cells	[202]
PDMS	-	Fibronectin deposited on the polymer	Film scaffold	Enhances cell behavior and candidates it for replication of a native 3D environment	[232]
Poly(amino acid)	Bone TE	Cyclic phosphonate modification	Film scaffold	Improves cell adhesion	[233]
PCL	Bone TE	Physical incorporation of ginseng extract into PCL electrospun nanofibers	Electrospun nanofiber	Higher calcium content, alkaline phosphatase activity and higher mineralization of mesenchymal stem cells were observed	[220]
PHEMA	-	Cholesterol-modified and laminin deposition	Hydrogel	Facilitates mesenchymal stem cells attachment, but does not support cell spreading and proliferation	[234]
PCL	-	Modified by fusion protein VEGF-HGFI	Electrospun nanofiber	Enhances cellularization and Vascularization in vivo	[235]
PLA	-	Grafting collagen	Electrospun nanofiber	Enhances cell adhesion and cell spreading	[44]
PCL	Bone TE	Heparin-immobilized	Electrospun nanofiber	Decreases the initial cell viability of mesenchymal stem cells and enhances bone morphogenetic protein-2 release into the scaffold	[236]
Composite of PLGA and PLA-*grafted*	Bone TE	RGD-conjugated	Porous scaffolds	Enhances bone ingrowth	[237]

nano-HA					

4.4. Polymer blends

4.4.1. Combination of two or more synthetic polymers

The blending of two or more synthetic polymers is an effective strategy for the development of biomaterials with synergic physicochemical as well as biological features. The most common approaches for the preparation of these blends are solvent and melt processing [238, 239]. Melt processing is a versatile method for preparing polymeric blend scaffolds with 100% interconnected 3D microstructures. However, the blending ratio and the post-annealing process are affected significantly the pore size and porosity of the resultant scaffold [240, 241]. Besides melt processing, some strategies such as solid-state gas foaming, the pore size and porosity of the scaffold can be easily controlled by adjusting the gas foaming parameters [240].

In a successful attempt, Kim and co-works [225] fabricated a blend of poly[2-methacryloyloxyethyl phosphorylcholine (MPC)-*co*-*n*-butyl methacrylate (BMA)] (PMB30W) and poly(L-lactic acid) (PLLA) through a solvent mixing and evaluated its bio-absorption implants after subcutaneous implantation. Compared to the PLLA tubing, the PLLA/PMB30W tubing significantly reduced the thrombus formation during 30 days of implantation. Human peripheral blood mononuclear cells were cultured on the PLLA and the PLLA/PMB30W to compare inflammatory reactions. Enzyme-linked immunosorbent assay quantified substantially decreased pro-inflammatory cytokines in the case of the PLLA/PMB30W. Some other examples that employed a combination of two or more synthetic polymers for scaffolding are listed in Table **9**.

Table 9. Some examples of scaffolds fabricated through the combination of two or more synthetic polymers.

Composition	Target TE	Fabrication method	Form of scaffold	In vitro main findings	References
PLA-based blend with phospholipid polymer	Cardiovascular Stents	Blending	Film scaffold	Reduces thrombotic occlusion in vivo and Inflammatory reactions in vitro	[225]
PCL/PLA	-	Melt blending	Nanofiber	Enhances cell adhesion and proliferation	[242]
PLA/polystyrene (PSt)	Bone TE	Solid-state foaming and immiscible polymer blending	Porous scaffold	Enhances cell growth	[240]
PEG/PLA	Bone TE	Solvent casting and porogen leaching	Porous scaffold	Enhances cell growth	[243]
PCL/poly(*N*-vinyl-2-pyrrolidone)	-	Blending and electrospinning	Electrospun nanofiber	Improves cell attachment and spreading	[244]
PVA/poly(hydroxy butyrate)	Skin TE	Blending and electrospinning	Electrospun nanofiber	Promotes adhesion and the proliferation of HaCaT cells	[245]
PVA/Poly(vinyl pyrrolidone) (PVP)	-	Blending and electrospinning	Electrospun nanofiber	Enhances cells adhesion and proliferation	[246]
PVA-*co*-ethylene)/PLGA	-	Blending by solution casting	Porous scaffold	-	[21]
PVA/PVP blends incorporated with HAp and β-TCP bone ceramic	Hard TE	Blending and electrospinning	Electrospun nanofiber	Supports better cell adhesion and proliferation	[247]
PCL/poly(ethylene oxide) (PEO)	Cardiovascular TE	Melt blending	3D plotted scaffold	-	[248]

β-TCP*: β*-tricalcium phosphate

4.4.2. Combination of synthetic and natural polymers

The blending of synthetic and natural polymers (bio-artificial blending) is a versatile approach toward more efficient biomaterials with enhanced physicochemical (*e.g.,* hydrophobicity) as well

as biological (*e.g.,* biocompatibility) features. This concept has been extensively discussed above (Section **2.2.2**).

4.5. Mineralization

Similar to natural polymers, the synthetic polymers can be also modified using mineralization strategy in order to improve mechanical as well as biological features of the final scaffold. Bio-mineralization is extensively used in bone TE. In this context, HA is the major mineral component in a native bone ECM, and a lot of calcium phosphate coatings appear to have the effective promotion of bone tissue regeneration. Therefore, the growth of calcium phosphate materials onto the surface of polymeric materials is an efficient strategy in order to provide osteoconductivity and osteoinductivity [119, 249].

Kokubo and colleagues [250, 251] developed a biomimetic process to form a calcium phosphate coating onto a surface modified substrate through the immersion into simulated body fluid (SBF) at physiological temperature, that has a composition similar to that of the human blood plasma. Qu and coworkers [252] studied the effect of oxygen plasma treatment on the formation of a bone-like apatite layer on PLGA films and scaffolds by incubation in modified SBF. The SEM micrographs of the scaffolds are shown in Figure **2**. It was revealed that the bone-like apatite formability of PLGA enlarged with increasing plasma-treating time. The surface chemistry plays an important role in the formability of apatite, thus, many research attempts have been devoted to improving the interface of apatite with substrates.

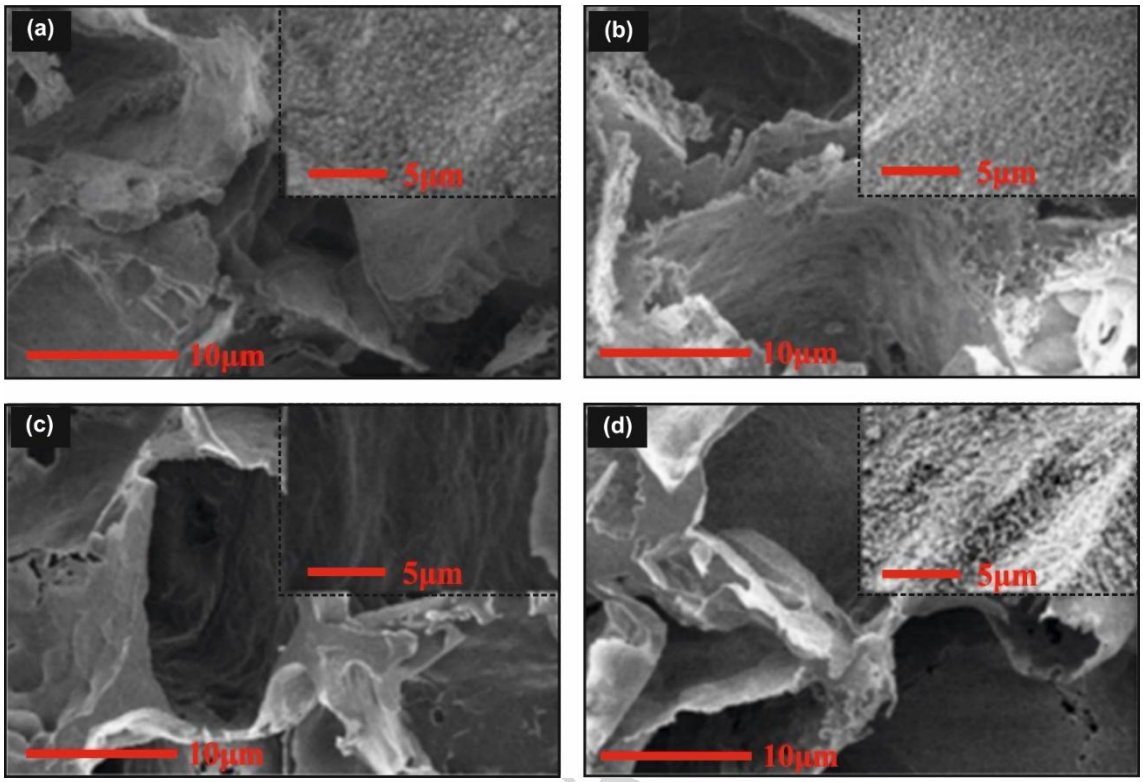


Figure 2. SEM micrographs of untreated and oxygen plasma-treated PLGA(70/30) scaffolds (treated at 20W for 30 min) after incubation in 1.5SBF0 for 6 days. (a) Untreated, surface; (b) plasma-treated, surface; (c) untreated, cross section; (d) plasma-treated, cross section [252].

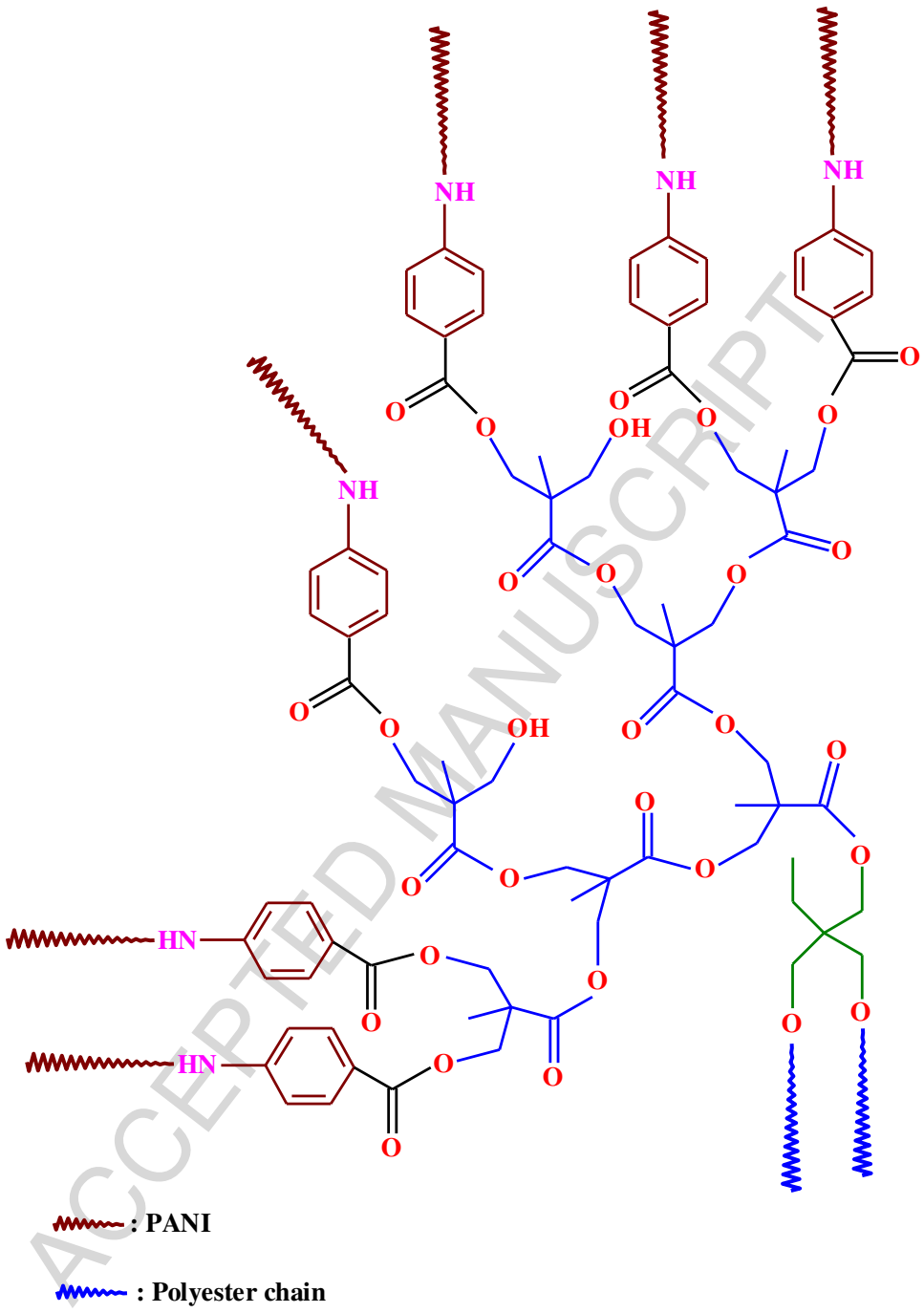
5. Electrically conductive biomaterials

It is well documented that normal biological functions in the human body (*e.g.,* signaling of the nervous system, muscle contraction, and wound healing) are needed to bioelectricity. Given this fact, the applying electrical stimulation (ES) through the scaffold can be modulate cellular activities including, cell migration, cell adhesion, cell differentiation, DNA synthesis, and protein secretion especially in the case of electrically excitable cells such as fibroblasts, osteoblasts, myoblasts, neural crest cells, and chick embryo dorsal root ganglia [253-255]. Thus, electrically conductive biomaterials can be considered as a potential candidate for scaffolding. These

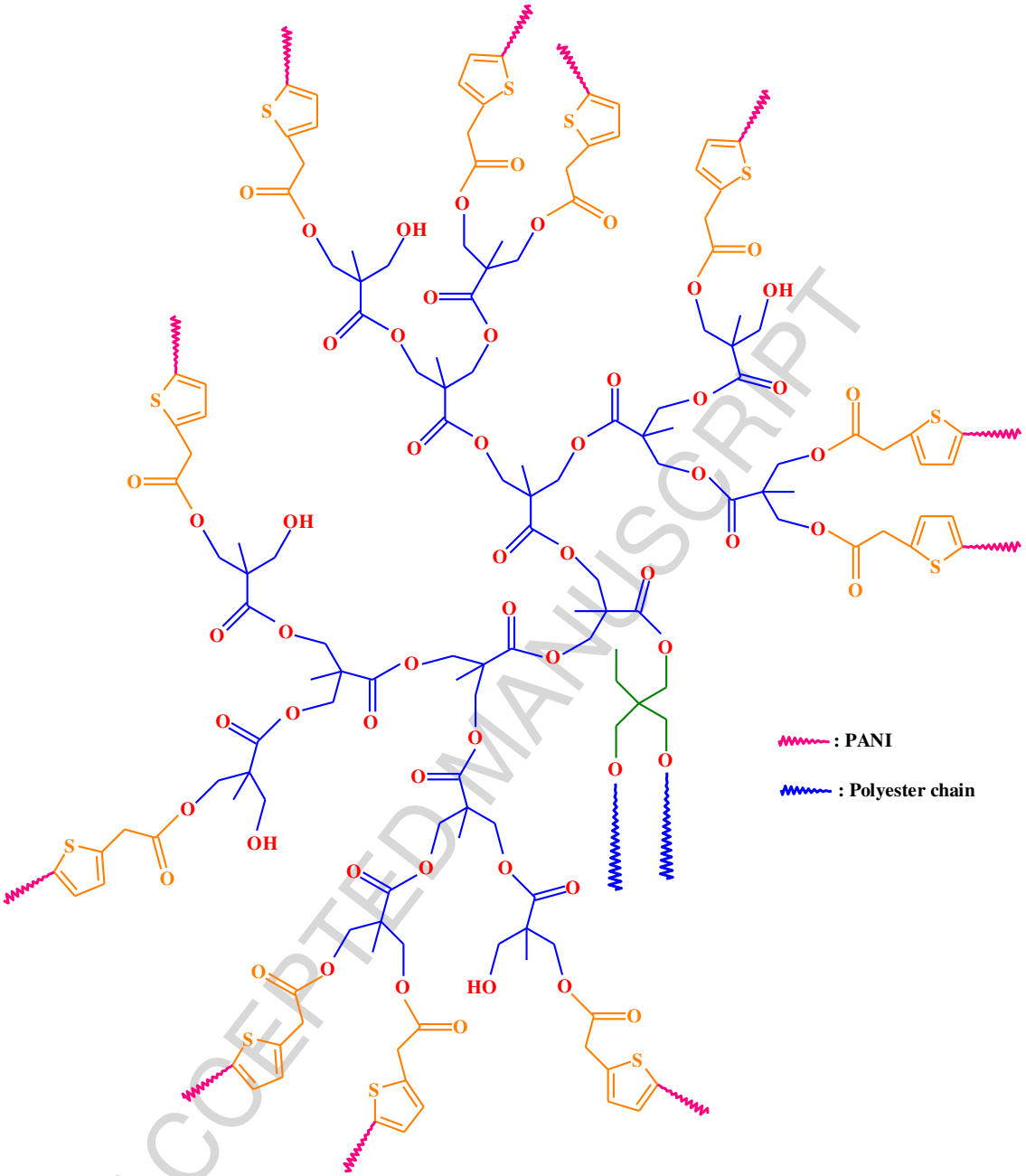
materials should be biodegradable, biocompatible, and have long-term ES or electrical stability. In this context, some researchers attempt to prepare electrically conducting scaffolds through the incorporation of conductive (nano-)particles such as carbon-based materials (*e.g.,* carbon nanotube [256, 257], graphene [258, 259]), and gold nanowires [260, 261] in implantable polymeric scaffolds. However, it is indeed admitted that these systems are non-biodegradable and possess long-term effects on fillers *in vivo*. This may cause tissue damage and aggravate inflammatory responses.

In this context, other types of synthetic polymers, namely electrically conducting polymers (ECPs) are proposed to overcome mentioned thematic issues [203, 262]. The intense interest in the use of ECPs expanded greatly from the 1980s when it was found that these polymers were compatible with many biological systems [143]. Among these, polyaniline (PANI), polypyrrole (PPy), polythiophene (PTh) and their derivatives are leading candidates in part due to their cell and tissue compatibilities both *in vitro* and *in vivo* after chemical modification or preparation of their blends with natural, synthetic and semi-synthetic polymers[263-266].

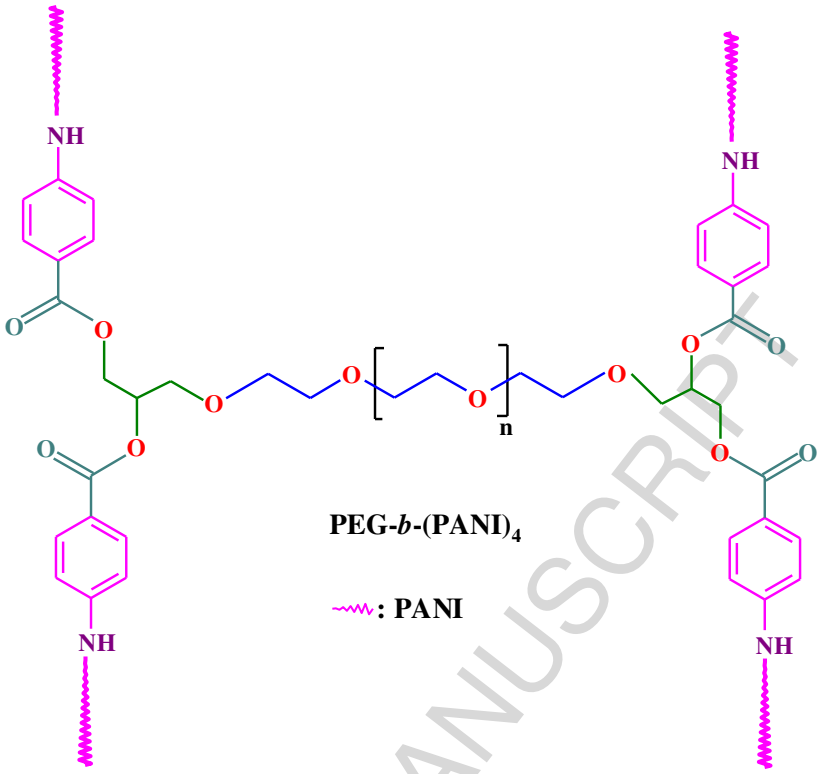
Many research groups including our laboratory fabricated electrically conductive biomaterials processes excellent electroactivity, biocompatibility, and biodegradability as scaffolds. Schemes **4**, **5**, **6**, and **7** present the structures of some chemically modified ECPs as scaffolding biomaterials, which fabricated by our research group.



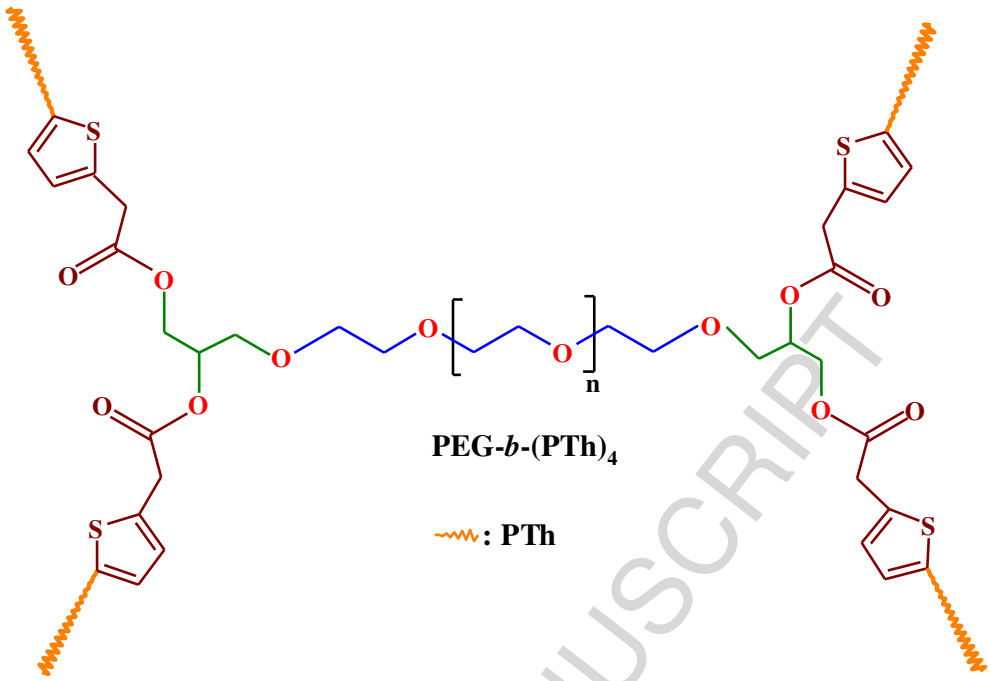
Scheme 4. The chemical structure of polyester-modified PANI [262].



Scheme 5. The chemical structure of polyester-modified PTh [203].



Scheme 6. The chemical structure of PEG-modified PANI [6].



Scheme 7. The chemical structure of PEG-modified PTh [4].

In addition, so many other successful research projects have been conducted and some convincing data have been obtained as summarized in Table **10**.

Table 10. Some examples of PANI, PPy, and PTh-based biomaterials which has been applied in the different area of TE.

ECPs	Composition	Form of scaffold	Target TE	Fabrication method	*In vitro* main findings	References
PANI	3-Aminobenzoic acid-PLA	Nanofiber	-	Electrospinning	Enhances cell growth	[267]
	PCL	Nanofiber	Skeletal muscle	Electrospinning	Conductivity enhances myotube maturation	[268]
	PCL/Gel	Nanofiber	Nerve	Electrospinning	Conductivity enhances cell proliferation and neurite outgrowth	[269]
	PCL/SF	Nanofiber/hydrogel	Skeletal muscle	Electrospinning/photo-cross-linking	Guides the myoblast alignment and differentiation	[270]
	Amyloid nanofibers	Core-shell nanowire	-	Template polymerization in the presence of amyloid nanofibers	-	[271]
	Chitin	Nanofiber	-	Electrospinning	Cytocompatible	[272]
	Gel	Nanofiber	Cardiac	Electrospinning	Stimulates the differentiation	[273]
PPY	*N*-Hydroxyl succinimidyl ester	-	Neuronal	Electrochemical synthesis	Improves neuritic network development	[274]
	Neurotrophin	-	Neuronal	Electrosynthesis	Improves neuritic network development	[275]
	PCL	Nanowire	Neuronal	Nanotemplating technique	Facilitates *in vitro* neural stem cell line adhesion, proliferation and differentiation	[276]
	PCL/Gel	Nanofiber	Cardiac	Electrospinning	Promote cell attachment, proliferation, interaction, and expression of cardiac-specific proteins	[277]
	PLGA	Nanofiber	Neuronal	Electrospinning	Supports neurite formation and neurite outgrowth	[278]
	PLA	Fluffy nanofiber	Neuronal	Electrospinning	Provides cell 3D-culture, improves cell growth	[279]
	PLA/Hep	Membrane	Bone	Blending and solvent casting	Enhances cell differentiation	[280]
	PLA	Film	Neuronal	Polymerization and co-precipitation	Supports neurite formation and neurite outgrowth	[281]

	Gel/CS graphene	Porous nanocomposite	Neuronal	*In situ* chemical oxidative polymerization	Cytocompatible	[282]
	Xanthan	Porous film	-	Electropolymerization	Supports cell adhesion and proliferation	[283]
	PDMS	Wrinkle film	Neuronal	Swelling-deswelling process	Promotes cell adhesion and neurite outgrowth	[284]
PTh	-	Films and fiber	Skeletal muscle	Electrospinning	Enhances cell proliferation and myotubes differentiation	[285]
	Poly(tetramethylene succinate)	Nanomembrane	-	Spin-coating	Enhances adhesion and proliferation of cells	[286]
	Poly(tetramethylene succinate)	Nanomembrane	-	Spin-coating	Cytocompatible	[287]
	-	Hydrogel	Skeletal muscle	Covalently cross-linking	Enhances adhesion and proliferation of cells	[288]
	Poly(3-hydroxybutyrate-*co*-valerate)	Film	-	Solvent casting	Less toxicity	[289]

2-HEC: 2-hydroxyethylcellulose; PLA: poly(lactic acid); PCL: poly(ε-caprolactone); Gel: gelatin; SF: silk fibroin; PP: polypropylene; Col type I: collagen type I; PU: polyurethane; PLGA: poly(lactic acid-*co*-glycolic acid); Hep: heparin; CS: chitosan; PDMS: poly(dimethyl siloxane)

6. Conclusions and future remarks

It is an unquestionable fact that natural acellular tissues in the body (*e.g.,* heart, kidney and bladder scaffold) are the best tissue scaffolds for regeneration of failed organs. However, the limitation of the sources is the most drawback of these scaffolds. In this context, naturally occurring biological macromolecules and synthetic (bio-)polymers are promising alternative materials for scaffolding. However, both natural and synthetic polymers have some drawbacks that should be solved before the application for TE. In this context, some strategies have been developed for improving the physicochemical as well as biological features of both polymer types.

In comparison with natural polymers, synthetic biopolymers have some advantages including, engineerable and tunable hydrophilic/hydrophobic ratio, degradation rate and mechanical characteristics. Nevertheless, their main drawback is lack of biological features. Due to poor mechanical as well as some negative physicochemical properties (*e.g.,* degradation rate and hydrophilic/hydrophobic ratio) of the most natural polymers, modification of these polymers seems to be necessary for the biomedical application. Thus, the design and development of new synthetic or semi-synthetic methodologies or physical approaches for modification of natural polymers to produce scaffolding biomaterials with proper physicochemical and biological features are necessary for further developing this context.

It seems that in comparison with naturally occurring polysaccharides and polyesters, the animal- or vegetable-derived polypeptides have higher performance as scaffolding materials. In this context, silk fibroin, collagen, and gelatin are of particular interest mainly due to their ability to mimic ECM. Therefore, it is expected that more research efforts should be focused on the fabrication of tissue scaffolds based on polypeptides.

Chemical modification of natural and synthetic polymers can be considered as a powerful tool for improving the physicochemical, mechanical as well as biological characteristics of these polymers. In the case of synthetic polymers, this approach improves hydrophilicity, biocompatibility, vascularization and surface density of functional groups.

Crosslinking strategy is another efficient and facile approach toward proper scaffolding biomaterials in the case of both natural and synthetic polymers. However, some crosslinking agents (*e.g.,* glutaraldehyde) lead to increase cytotoxicity in some cases. Therefore, design and development of green chemicals and more efficient crosslinking approaches are necessary to obtain crosslinked biomaterials with appropriate physicochemical as well as biological characteristics for TE applications. The cytotoxicity issue can be solved through the use of physical and enzyme-catalyzed crosslinking approaches, and produce safer biomaterials. Despite, the crosslinking efficiency may be reduced in comparison with chemical crosslinking. Therefore, development of more efficient enzymatic crosslinking agents is required to achieve biomaterials with acceptable physicochemical as well as biological features.

The blending of polymers is an additional efficient approach that can improve the physicochemical and mechanical features of natural polymers as well as cytocompatibility issue in the case of synthetic polymers. These polymeric biomaterials can be produced through the combination of natural polymers, natural and synthetic polymers, and synthetic polymers toward biomaterials with synergic physicochemical as well as biological features. In addition, these biomaterials are safe and without any chemical or biological contamination.

Mineralization strategy has received more and more interest due to the synergic effects on mechanical as well as biological (*e.g.,* protein adsorption and subsequent cell adhesion) features of the final scaffold. Furthermore, this approach may lead to the sustained release of growth

factors and genes. This approach involves the incorporation of inorganic materials such as HA, bio-silica, metalloenzymes (known as alkaline phosphatase; ALP), and bioactive glasses on the surface of the scaffold. This strategy is extensively used in bone or dental TE. The most important approach toward the mineralization is the immersion of scaffold into simulated body fluid (SBF).

The physical modification is a promising approach toward improving physicochemical as well as biological features of both natural and synthetic polymers. This modification technique is simple, cheap and safe, because it requires no chemical or biological agents. This approach can easily manipulate the stiffness, roughness, and topography of polymeric scaffold that influence the cell adhesion and proliferation. The most important advantages of physical modification are a mild condition in the most cases, more environmental friendly due to the lack of any chemical or biological agents, no undesirable changes in the polymer surface morphology, simplicity, scalability, more cost-effectivity (in most cases), and applicability for a huge range of natural or synthetic polymers.

It is well established that the size of scaffold has a pivotal role in TE performance, thus it is expected that more research efforts focused on the design and development of nano-sized polymeric scaffolds besides their modifications. In these types of scaffolds, cell-materials interactions increased significantly in comparison with micro-structured scaffolds, and lead to better cell adhesion and *neo*-tissue formation. In this context, nanofibrous scaffolds can be considered as nano-sized and porous substrates that could be produced through phase separation and electrospinning techniques. On the other hand, native ECM is the optimized milieu, which nature has been developed to maintain homeostasis and to direct tissue development. Therefore, a considerable of research effort has been focused to imitate the native ECM to guide

morphogenesis during TE. In this context, some promising results have been obtained using the fabricated scaffolds by electrospinning technique.

Great research efforts have been done for design and developing the smart naturally derived systems in last decade. The most important advantages of these systems are novel degradable matrix through adequate cell signals and actions, self-assembling systems that can be tuned by external signals, fabrication of new injectable thermogelling materials that could be used to deliver cells or growth factors through non-invasive approaches. In addition, stimuli-responsive hydrogels as scaffolds can deliver bioactive agents in response to stimuli trigger (*e.g.,* temperature, pH, ionic strength or presence of specific enzymes). Despite some convincing data that obtained using mentioned systems, more integration of synthetic technologies and biological science is necessary to design and development of novel and more efficient multifunctional biomaterials in the future.

It is the authors' opinion that stem cells are the best and the first choice for a successful TE, mainly due to their inherent biological features including, osteogenic, self-renew and differentiate into neurogenic, chondrogenic, as well as myogenic lineages under appropriate stimuli from extracellular components. Thus, more works are needed to investigate polymeric materials-stem cells interaction during tissue regeneration.

In conclusion, the promising results are available in the literature regarding the use of natural and synthetic polymers as well as their combinations as scaffolding biomaterials, however, many improvements should be made to investigate the effects of the cell types, growth factors, scaffold features, and other unknown physicochemical as well as biological characteristics on the fate of final artificial tissues in a successful TE.

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Competing interests

The authors declare that they have no competing interests.

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Abbreviations

3D: three-dimensional

ALP: alkaline phosphatase

ATRP: atom transfer radical polymerization

CaPs: calcium phosphates

CMC: carboxymethyl cellulose

CS: chitosan

ECM: extracellular matrix

ECPs: electrically conducting polymers

ES: electrical stimulation

GAG: glycosaminoglycan

HA: hydroxyapatite

HAP: hyperbranched aliphatic polyester

hMSCs: human mesenchymal stem cells

HRP: horseradish peroxidase

HUVEC: human umbilical vein endothelial cell

HwjhMSC-MT: human Wharton's jelly MSC micro-tissue

NMRP: nitroxide-mediated radical polymerization

PANI: polyaniline

PBS: poly(butylene succinate)

PCL: poly(ε-caprolactone)

PDMS: poly(dimethylsiloxane)

PEO: poly(ethylene oxide)

PGA: poly(glycolic acid)

PHEMA: poly(2-hydroxyethyl methacrylate)

PLA: poly(D, L-lactide)

PLCL: poly(L-lactide-*co*-ε-caprolactone)

PLGA: poly(lactic-*co*-glycolic acids)

PLLA: poly(L-lactic acid)

PMB30W: poly[2-methacryloyloxyethyl phosphorylcholine (MPC)-*co*-*n*-butyl methacrylate (BMA)]

PNIPAAm: poly(*N*-isopropylacrylamide)

PPy: polypyrrole

PTh: polythiophene

PU: polyurethane

PVA: poly(vinyl alcohol)

RAFT: reversible addition of fragmentation chain transfer

RDRP: reversible-deactivation radical polymerization

ROP: ring-opening polymerization

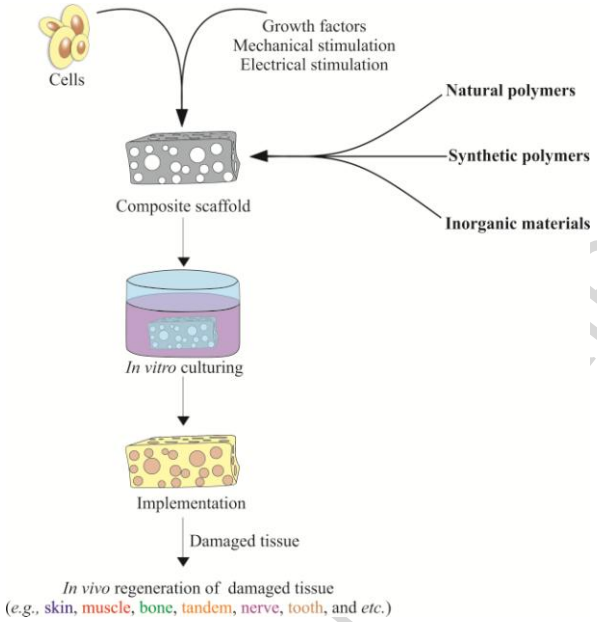
SBF: simulated body fluid

SF: silk fibroin

TE: tissue engineering

TPU: thermoplastic polyurethane

Graphical abstract



This review is the first up-to-date comprehensive overview regarding the employing of natural and synthetic polymers or their composites as well as copolymers for scaffolding.

Highlights

1. An overview of synthetic and natural polymers-based scaffolding biomaterials
2. Physicochemical and biological features of scaffolding biomaterials
3. Fundamentals and general characteristics of natural and synthetic polymers
4. Modification approaches of synthetic and natural polymers for scaffolding
5. An impetus for the development of novel multifunctional scaffolding biomaterials

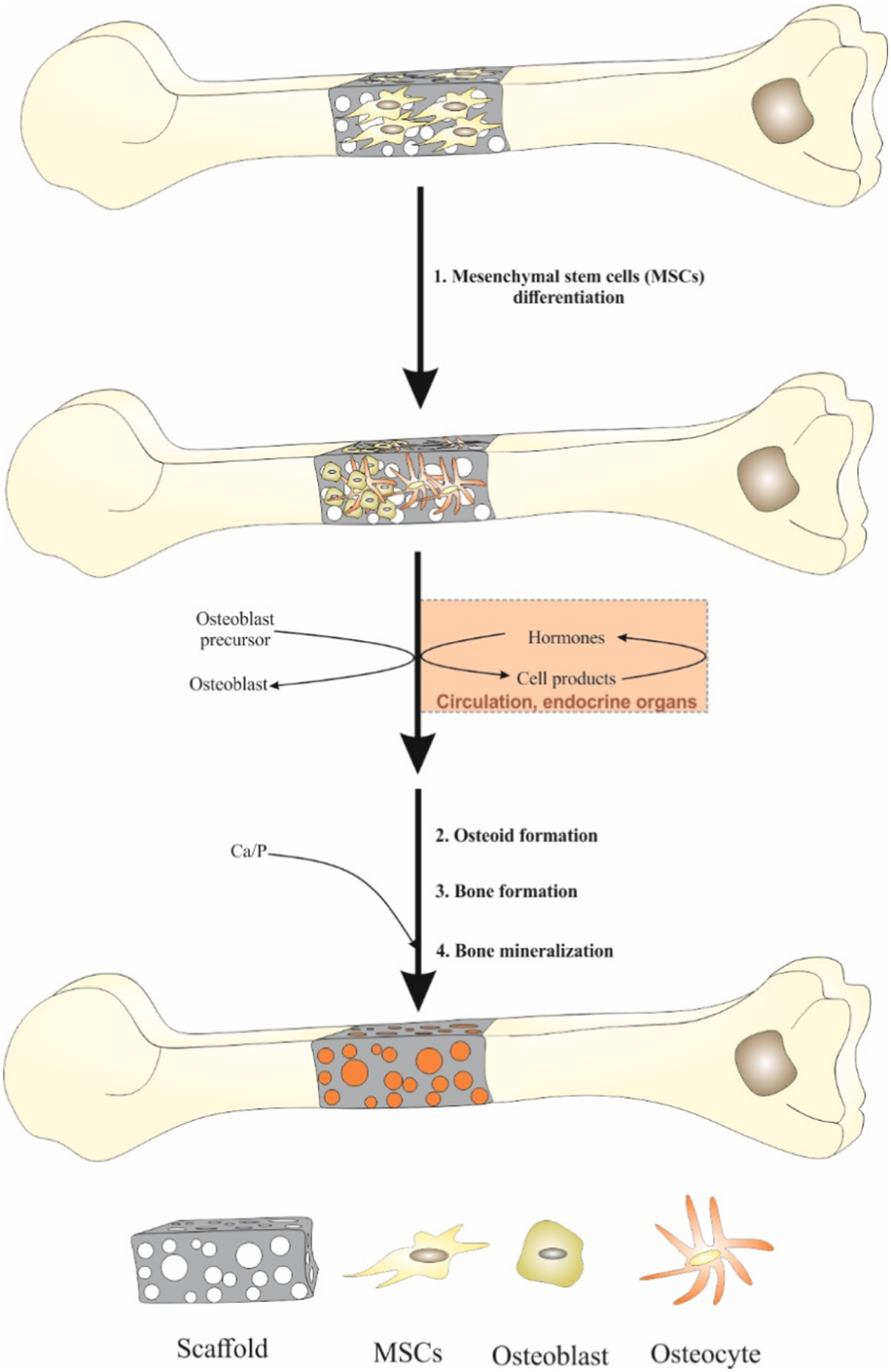

1. Mesenchymal stem cells (MSCs) differentiation
Osteoblast precursor
Osteoblast
Hormones
Cell products
Circulation, endocrine organs
Ca/P
2. Osteoid formation
3. Bone formation
4. Bone mineralization
Scaffold
MSCs
Osteoblast
Osteocyte

Figure 1

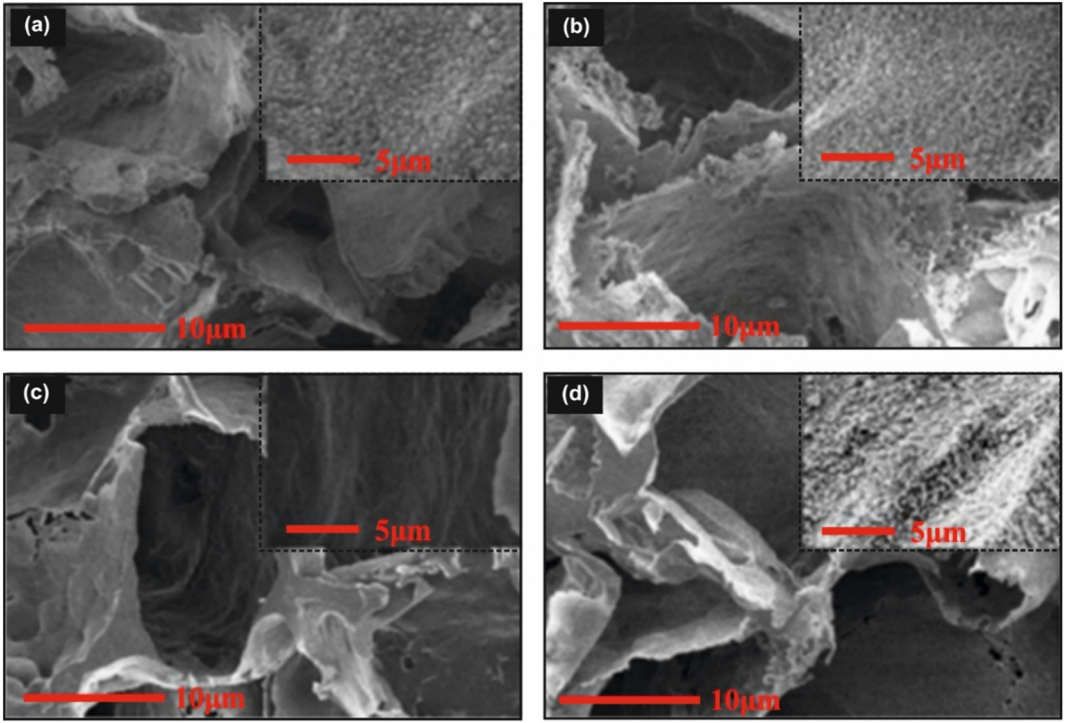


Figure 2