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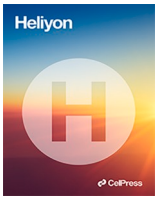

Review article

Application of gelatin-based composites in bone tissue engineering

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ABSTRACT

Natural bone tissue has the certain function of self-regeneration and repair, but it is difficult to repair large bone damage. Recently, although autologous bone grafting is the "gold standard" for improving bone repair, it has high cost, few donor sources. Besides, allogeneic bone grafting causes greater immune reactions, which hardly meet clinical needs. The bone tissue engineering (BTE) has been developed to promote bone repair. Gelatin, due to its biocompatibility, receives a great deal of attention in the BTE research field. However, the disadvantages of natural gelatin are poor mechanical properties and single structural property. With the development of BTE, gelatin is often used in combination with a range of natural, synthetic polymers, and inorganic materials to achieve synergistic effects for the complex physiological process of bone repair. The review delves into the fundamental structure and unique properties of gelatin, as well as the excellent properties necessary for bone scaffold materials. Then this review explores the application of modified gelatin three-dimensional (3D) scaffolds with various structures in bone repair, including 3D fiber scaffolds, hydrogels, and nanoparticles. In addition, the review focuses on the excellent efficacy of composite bone tissue scaffolds consisting of modified gelatin, various natural or synthetic polymeric materials, as well as bioactive ceramics and inorganic metallic/non-metallic materials in the repair of bone defects. The combination of these gelatin-based composite scaffolds provides new ideas for the design of scaffold materials for bone repair with good biosafety.

1. Introduction

Bone is a connective tissue composed of non-homogeneous composites that performs a variety of important functions in the body, including movement, support and protection. It functions as a repository for calcium and phosphorus, with its structure primarily composed of a mineral phase known as hydroxyapatite (HAp) alongside and organic phase [1,2]. In addition, the extracellular matrix composition of bone is mainly 85%–90% type I collagen, 5% non-collagenous proteins, 2%–5% lipid and water [3]. In case of skull bone defects less than 8 mm in rat, bone tissue possess the capability to regenerate and self-heal [4]. However large traumas or bone defects caused by tumors, congenital diseases, osteomyelitis, etc., autogenous or allogeneic tissue need to be filled to promote bone healing [5,6]. Autologous bone grafting is considered the gold standard in clinical treatment for bone defect repair. However, it faces

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several challenges, such as limited bone supply, the risk of disease transmission, and the difficulty of clinical treatment [7,8]. Bone tissue engineering(BTE) is considered an important optimal choice for the development of regenerative bone grafting and repair [9]. BTE consists of three key elements: bone tissue scaffolds, seed cells, and growth factors. The construction of bone scaffolds is a hot and difficult research topic in bone tissue engineering [10,11]. Bone scaffold materials not only need high mechanical properties to support bone defects, but also serve as a medium for information transfer between bone cells, it provides an optimal microenvironment that fosters the growth and proliferation of bone cells as well as facilitates the process of biomineralization [12,13].

Optimal bone scaffold materials should have structural properties similar to natural bone tissue, including excellent biocompatibility, mechanical properties, appropriate porosity and biodegradability [14,15]. Gelatin, a natural polymeric material, has gained widespread application in bone tissue engineering due to its unique properties [16]. The gelatin is obtained by hydrolysis of collagen, and its most abundant sources are pig skin, cow skin, pig bone, and bovine bone. Gelatin is widely used as a drug delivery system for osteogenic active molecules and as a scaffold material [17]. The unique arginine-glycine-aspartate (RGD) sequence of gelatin provides for the promotion of cell adhesion, proliferation and differentiation [18]. In addition, gelatin can be prepared into shapes such as nanofiber scaffolds, hydrogels, and nanoparticles through 3D printing, electrostatic spinning, freeze-drying, and other techniques to better accommodate different shapes of bone defects [19,20]. Fig. 1 shows the process of gelatin-based 3D scaffolds for BTE. The disadvantages of gelatin are also obvious, it is not able to be used for culturing cells alone and has poor mechanical properties, which are not sufficient to be used as a scaffold material. The nature of gelatin as an osteoblast-like matrix analogs and other excellent properties have been fully utilized with the introduction of BTE [21,22]. Currently, due to the easy modification of gelatin, it is commonly used for compounding with various natural polymer materials, synthetic materials as well as inorganic materials such as bioactive ceramics and metal/non-metal inorganic compounds [23,24]. Therefore, modified gelatin or composites with synergistic effects of different physiological functions can be prepared, which not only have high mechanical properties, but also osteoinductive activity and bone microenvironmental regulation [25,26].

The review delves into the fundamental structure and unique properties of gelatin, and the excellent properties necessary for bone scaffold materials. Then comprehensively explores the application of modified gelatin 3D scaffolds with various structures in bone repair, including 3D fiber scaffolds, hydrogels, and nanoparticles. The paper primarily reviews the exceptional effectiveness demonstrated by composite bone tissue scaffolds composed of modified gelatin and various natural or synthetic polymeric materials, as well as bioactive ceramics and inorganic metal/non-metal materials, in the repair of bone defects. This review provides new perspectives and ideas for gelatin research in the field of BTE.

2. Structure and properties of gelatin and bone scaffold materials

2.1. Structure and properties of gelatin

Gelatin is obtained by partial hydrolysis of insoluble collagen originating from pigs, cows, fish, etc., followed by pretreatment and extraction procedures [27,28]. Gelatin can be categorized into different types based on different preparation processes. Among these, collagen is treated by acid to obtain type I gelatin, which has an isoelectric point (PI = 8–9), while type II gelatin obtained by treatment with alkali has an isoelectric point (PI = 4–5) [17,29]. These differences stem from the different chemicals used in the treatment process, resulting in subtle changes in gelatin properties. Furthermore, controlling the temperature during the processing allows the triple-helical collagen to be fragmented into gelatin with different molecular weights, thus producing gelatin with varying degrees of mechanical strength [16,30,31]. Due to its excellent biocompatibility, biodegradability, low toxicity, and low allergenicity, gelatin has emerged as an ideal choice for bone tissue scaffold materials [32,33]. Furthermore, as an analogue of the extracellular matrix, gelatin possesses a unique RGD sequence, as shown in Fig. 2, which provides a favorable biological environment for bone cell adhesion, proliferation, and biomineralization [34,35].

2.2. Structure and properties of bone scaffold materials

In order to successfully repair and support the bone regeneration process, a good bone scaffold material should have structural

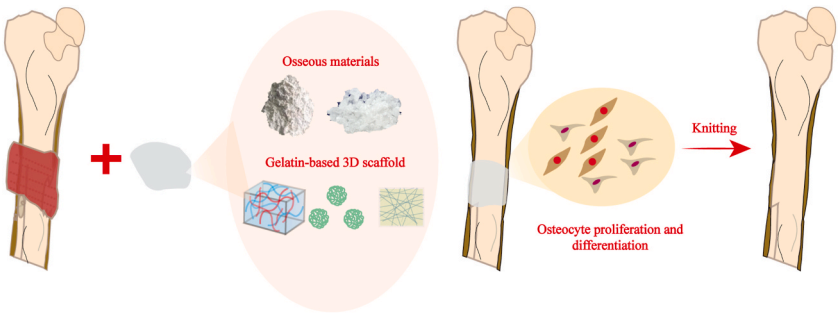

Fig. 1. Gelatin-based 3D scaffold for BTE.

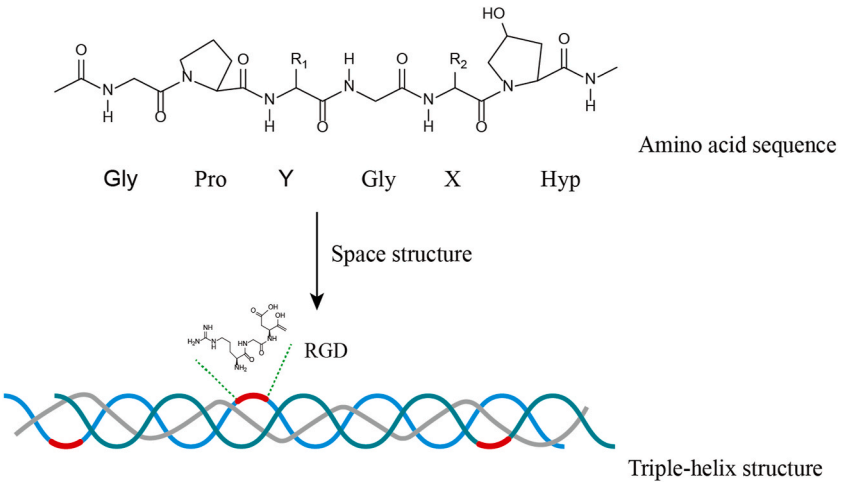

Fig. 2. Constitution and structure of gelatin.

properties similar to those of natural bone, including good biocompatibility, biodegradability, porosity and mechanical strength. Moreover, it should have good cell adsorption and tissue adhesion, which is conducive to the proliferation and differentiation of seed cells and osteogenic regeneration [36,37].

The degradation rate of bone scaffolds had an important influence in the process of bone repair. Too fast degradation rate will lead to the bone scaffold unable to support the proliferation of host cells of bone tissue, resulting in the obstacle of new bone regeneration, while too slow degradation rate will be unable to make enough space for the regeneration of new bone, which is not conducive to the continuous regeneration of bone tissue [38]. Therefore, the rate of explanation of bone scaffolds should match the rate of new bone regeneration. For example, Tariq et al. prepared composite scaffolds using gelatin and PCL as the main materials by electrostatic spinning technique, which showed that the single PCL scaffold had no degradation in 28 days, while the introduction of hydrophilic gelatin resulted in the degradation of its composite scaffolds from day 7 to day 28 at a rate of ~31 %–~68%, which was matched with the average periosteum recovery time of 2–4 weeks, respectively [39]. Under the action of matrix metalloproteinase (MMP) in vivo, gelatin molecules were degraded to collagen fragments and tripeptides, and several studies have been conducted to show that gelatin not only possesses excellent biocompatibility, but its degradation products are also beneficial in promoting bone repair. For example, Hatakeyama et al. cultured human umbilical vein endothelial cells (HUVECs) with gelatin degradation products, which showed that gelatin degradation products significantly promoted the formation of capillary-like structures in HUVECs, stimulating angiogenesis and bone regeneration [40].

The porosity, mechanical strength and shape of bone scaffolds affect the bone repair process to varying degrees as well [41]. Porosity was a key element in evaluating whether the bone scaffold had the performance of new bone molding. Too high porosity leaded to lower mechanical strength of the scaffold, while too low porosity might be detrimental to the growth of new osteoblasts and vascularization of tissues. The proper porosity and pore size distribution played a key role in osteoblast attachment, migration, regeneration, as well as nutrient and metabolic waste transfer [42]. The small pore size (≈100 μm) bioscaffolds have been shown to be effective for in vitro bone tissue regeneration in cultured bone, with interconnected pores capable of meeting the oxygen, nutrient, and cell attachment requirements of the bone regeneration process. While larger pore sizes (≥300 μm) have also been found to have good tissue permeability, allowing for vascularization within the body, which is beneficial for bone regeneration [43,44]. The optimal scale of porosity and mechanical strength has been a challenge for scaffold materials. Porosity and mechanical strength similar to bone composition were able to have a more positive impact on the bone repair process [45]. El-Bahrawy et al. prepared gelatin composite scaffolds with porous hybrid structure by adjusting different gelatin/PVA ratios, which showed that gelatin/PVA porous hybrid scaffolds not only had the high porosity and pore size, but also the mechanical properties were close to the compressive strength of cancellous bone, and the scaffolds had the potential to repair the damage of cancellous bone [46].

3. Gelatin 3D scaffold

From the bionic perspective, scaffold materials for bone tissue engineering require a 3D structure [47].To mimic the complexity of the extracellular matrix structure and to promote normal cell growth, many scaffold fabrication techniques, such as solvent casting, particle leaching, gas foaming, phase separation, freeze-drying, self-assembly, and electrostatic spinning, have been developed for gelatin 3D scaffolds [48–50]. Gelatin 3D scaffolds not only provided mechanical support and microenvironment for osteoblasts, but also, compared with traditional tissue engineering, cell-based strategies of gelatin-based scaffold materials were currently attracting a lot of attention by carrying progenitor cells, cytokines, or biologically active molecules in order to achieve the recruitment of cells and accelerate the induction of new bone regeneration [51,52]. MSCs with differentiation ability were the most ideal seed cells for tissue engineering. MSCs were able to be closely integrated with gelatin scaffolds and implanted into bone injury sites to effectively stimulate

the regenerative and osteogenic differentiation effects of bone cells [53]. Cytokines or bioactive molecules and gelatin scaffolds were adsorbed and mixed through the scaffolds, leading to a slow release, which were widely used in bone repair. Three cytokines, BMP-2, BMP-7 and PGDF-BB, which have been clinically approved for use in bone grafts for the treatment of hard-to-heal bone repair surgery [54]. There are three main types of gelatin 3D scaffolds (Fig. 3), which are nanofiber scaffolds, hydrogels and nanoparticles [55,56].

3.1. Nanofiber scaffold

Nanofiber scaffolds with a 3D porous structure provide a supportive matrix for cell attachment, differentiation, and new bone formation [57,58]. The scaffolds have a high specific surface area, increasing the ability of the scaffolds to attach a large number of cells. Scaffolds with varied pore sizes are fabricated by various methods such as freeze-drying and electrostatic spinning [59,60]. Scaffolds with pore sizes of 200 μm facilitate bone regeneration because they facilitate nutrient transport and metabolite drainage, as well as provide space for new bone formation and vascularization [61]. The mechanical properties of nanofiber scaffolds should be similar to those of natural tissues to protect cells from tensile forces. Electrostatic spinning is currently the most widely used method for fabricating nanofiber scaffolds [62,63]. Within this method, a polymer solution is mixed with an appropriate volatile solvent and loaded into a syringe. The polymer is ejected under mechanical pressure, when a voltage is applied, the droplet at the needle changes from a sphere to a cone (Taylor cone) and extends from the tip of the cone to obtain fibrous filaments, which pile up in a reciprocal manner to form a porous scaffold [64,65]. The size of the pores in the scaffolds is changed by varying the current, flow rate, voltage, and the distance between the collection plate and the syringe. For example, Sneh et al. prepared Gelatin-PCL-nHAp nanocomposite scaffold materials by electrostatic spinning technique, which showed a significant increase in cell survival rate and enhanced cell adhesion and proliferation [66].

3.2. Hydrogel

Hydrogel is a polymeric material with a 3D mesh structure which can swell in water and retain a large amount of water [25,67]. Gelatin hydrogels contain a large number of hydrophilic groups such as hydroxyl, carboxyl and amino groups in the molecular chain segments which absorb a large amount of water to maintain the soft physical properties and provide more possibilities for modification [68,69]. Modified gelatin hydrogels can be prepared by physical cross-linking, enzymatic cross-linking, and chemical cross-linking [70]. The common methods for physical cross-linking are plasma, UV radiation and dehydrogenation heat treatment, which produce no potentially cytotoxic chemicals. However, the modified gelatin hydrogel network prepared by physical cross-linking has a low degree of crosslinking [71]. Chemical cross-linking can be achieved by adding a cross-linking agent to activate a gelatin molecule and the activated gelatin molecule is directly bonded to another gelatin molecule by chemical bonding, or the cross-linking agent is chemically bonded to the active functional group of the gelatin and is stabilized in that form in the structure of the gelatin [68,72]. Commonly used cross-linking agents include 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, EDC, aldehydes (such as formaldehyde, glutaraldehyde), epoxy compounds (such as ethylene oxide, glycidyl ether), plant polyphenols (such as tannic acid, ferulic acid), etc. Currently, enzyme cross-linking is mainly used for polymeric materials with glutamine aminotransferase, tyrosinase, and horseradish peroxidase. Enzyme cross-linking can not only improve the mechanical properties of modified gelatin scaffolds but also enhance their osteogenic effects, which forming a dense 3D network structure through cross-linking with amino acid residues of gelatin polymers without the use of chemical cross-linking agents and organic solvents [73,74].

Gelatin hydrogels can be used to protect cells as well as to load certain growth factors or functional drugs to promote bone tissue repair. In recent years, smart injectable hydrogels have received increasing attention because they can be used for minimally invasive treatments [75]. The smart injectable hydrogel system is a liquid at room temperature and forms a hydrogel when injected into the location of bone cracks to fill intricately shaped defects [2,76]. The smart injectable hydrogels are able to shorten surgery time, reduce pain after surgery, lessen scar size and allow patients to recover quickly in an economical way. For example, Zhe et al. utilized nano-HAp and nano-silicate (SN) compounded with gelatin to prepare MSC-loaded GelMA-HAp-SN composite hydrogel scaffold, which was able to activate the highest expression of new bone formation and vascularized tissue [77].

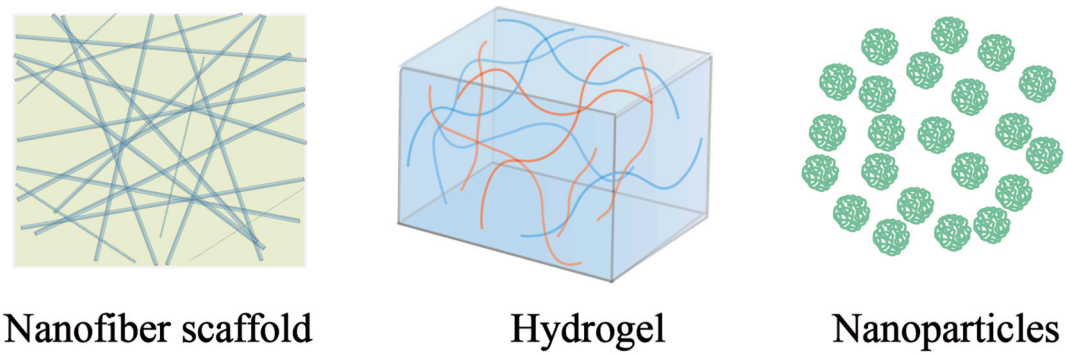

Fig. 3. Gelatin 3D scaffolds including nanofiber scaffolds, hydrogels and nanoparticles.

3.3. Nanoparticles

Nanoparticles are be used to deliver drugs and growth factors that exhibit excellent slow release with effective promotion of bone regeneration [78]. In addition, nanoparticles could modify the properties of scaffolds, such as superior mechanical properties and osteoinductive activity. For stance, Schrade et al. prepared an alginate dialdehyde-gelatin nanoparticle scaffold loaded with clindamycin and growth factors, which showed that the modified gelatin scaffold could effectively promote the proliferation of MG-63 cells and enhance the inhibition of staphylococcus aureus [79].

BTE is a rapidly developing field. The gelatin composite scaffolds have been widely studied in nanofiber scaffolds, hydrogels, and nanoparticles, in addition to the application of new technologies such as 4D scaffolds and organoids based on gelatin materials, which have demonstrated unique advantages in recent years [80,81]. 4D printing is based on the 3D structure to add a time dimension, so that the printed scaffold automatically changes over time with internal and external stimuli, with its unique responsiveness and shape change ability will better match the physiological environment of bone defects, which is expected to achieve a more accurate and individualized treatment [82]. However, in the process of bone repair was usually accompanied by the regulation of multiple cellular activities, the 4D printed scaffolds hardly were respond to multiple synergistic effects, so the design of 4D printed scaffolds with multiple stimulus responsed to meet the dynamic changes of the microenvironment in the process of bone repair is an important breakthrough point [83]. For example, Chakraborty et al. used SF-gelatin bioink doped with magnetic nanoparticles to achieve mechanically actuated and thermally responsive mechanical stimulation of cartilage regeneration under prolonged driving by a magnetic field [84]. Bone organoids are bionic bone tissues with spatial structure and capable of self-renewal through directed differentiation of stem cells, and are genomically stable in long-term expansion in vitro. Bone organoids were usually based on bioactive material scaffolds and extracellular matrices to provide strong mechanical supportt [85]. Wang et al. prepared GelMA/AlgMA/HAP Scaffolds loaded with bone marrow mesenchymal stem cells through 3D printing, through in vivo cultivation, the organoid formed trabecular-like structural features of bone by self-mineralization, and its mechanical properties were comparable to those of natural spongy bone [86]. However, bone organoids were influenced by the physiological microenvironment of normal tissues, the complexity and sophistication of neural networks, blood vessels and other physiological functions, as well as the normal developmental and maturation environment of osteoid organs has not been satisfied at present, which still need to be invested in more comprehensive research [87].

4. Modified gelatin and its composite materials

Given the abundance of readily modifiable groups in gelatin, such as hydroxyl, amino and carboxyl groups, gelatin-based scaffolds with excellent mechanical properties and outstanding osteoinductive activity can be successfully produced through clever modification by chemical reactions or physical methods [16,47]. These include the modification of gelatin with methacrylic anhydride (MA), dopamine, polyphenols, adipic dihydrazide and maleic anhydrideto optimize its properties for specific applications [88]. The structure of the compounds used for gelatin modification is shown in Fig. 4. And for example, Yang et al. prepared a hydrogel biomimetic periosteum by combining dopamine-modified gelatin with oxidized hyaluronan and doped with micro/nanobioactive glass, which showed excellent adhesion to bone tissue and formed a stable barrier in the region of bone defects [89]. Moreover, Honda et al. used epigallocatechin gallate (EGCG) for gelatin modification, which showed a significant increase in the degradation time of the scaffold and improved osteoinductivity of the scaffold material with significant bone repair effect [90].

Currently, gelatin-based bone scaffold materials are usually combined with various natural or synthetic polymeric materials as well as bioceramics and inorganic metallic/non-metallic materials to achieve synergistic effects and are widely used in the field of bone tissue engineering for their many performance advantages, such as more mechanical properties, osteoinductive activity, and anti-

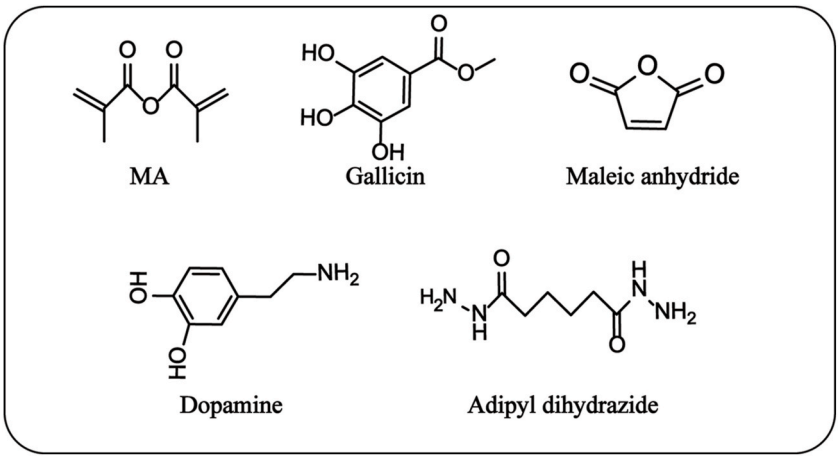

Fig. 4. The structure of the compounds used for gelatin modification.

infection [91–93].

4.1. Organic polymer materials

With the introduction of BTE techniques, gelatin-based materials are often composited with functional organic polymers, aiming to cope with the diverse and complex physiological demands faced during bone injury healing. The emergence of such composites, which often exhibit superior mechanical properties, as well as anti-inflammatory effects and low immunogenicity, has attracted close attention and in-depth studies by a wide range of researchers.

4.1.1. Natural polymer materials

Natural polymer materials generally have good biocompatibility and biodegradability, which not only promote the adhesion of osteoblasts to bone but also promote cell proliferation. Natural polymers include polysaccharide biomolecules, polyphenols, and protein polymers, which can modify gelatin by chemical surface modification, physical modification, or enzymatic cross-linking to improve the osteoinductive activity and mechanical properties of modified gelatin scaffold materials [94,95]. The major natural polymer bone scaffold materials that are commonly used for gelatin modification include chitosan (CS), Alg, silk fibroin (SF) and peptide.

CS, a product of chitin deacetylation, is similar in structure to glycosaminoglycan, the molecular chain is a copolymer composed of β-(1,4)-2-acetylamino-D-glucan unit and β-(1,4)-2-amino-D-glucan unit. Chitosan has good biocompatibility, biodegradability, and antibacterial activity. It is often used in various skin, nerve, and soft tissue engineering [96,97]. However, the mechanical properties and stability of single CS limit application of tissue engineering. Gel-CS based composites are obtained by chemical cross-linking [98]. The CS molecular chain contains abundant $–NH_2$ and –OH reactive groups, while the gelatin molecular chain contains $–NH_2$, –OH, –COOH reactive groups. Therefore, CS and Gelatin are cross-linked by covalent bonds to obtain Gel-CS based composites. What's importantly, compared with single gelatin or CS materials, the gelatin-CS composite scaffolds have significant advantages in porosity, swelling rate, degradation rate, mechanical properties, biomineralization and cell adsorption capacity [2,99]. For instance, Ranganathan et al. prepared Gel-CS composites, which showed significant superiority compared to single CS and gelatin in affecting the properties of bone regeneration [100]. Moreover, Gel-CS composites can be used as scaffold materials to load seed cells or growth factors for more efficient application in BTE.

SF is a natural polymeric fibrous protein extracted from silk, which can be obtained by degumming the natural silk [101]. SF with 18 amino acids and has amphoteric charge. Compared with other natural or synthetic fibers, it has unique mechanical properties, such as good flexibility, tensile strength and breathability, which has been widely used in the field of tissue engineering [102]. SF can be prepared into thin films, hydrogels, and porous sponge materials by using chemical or physical modification methods. In combination with gelatin, it can effectively compensate for the poor mechanical properties of gelatin and be better used in BTE. Gel-SF scaffolds have good mechanical properties, thermal stability and degradation rate, which can not only provide suitable mechanical support for traumatic bone injury, but also accelerate bone regeneration by adsorbing cells on the scaffold [103]. For example, Luetchfork et al. prepared a variety of Gel-SF scaffolds in different ratios, which supported the adhesion of MSCs with high efficiency compared to single Gel or SF, and had a broad therapeutic potential for bone injury repair [104].

Alg, a kind of natural polysaccharide polymers rich in β-D-mannuronic acid and α-L-guluronic acid structural fragments, is extracted from the brown algae kelp and Sargassum [105]. Alg shows the advantages of high hydrophilicity, good biocompatibility and biodegradability. However, Alg has the weak mechanical properties, lack of intercellular interaction and uncontrolled degradation. Compositing sodium alginate with gelatin is able to compensate the shortcomings of both sides and improve the utilization rate and therapeutic effect of bone defect repair [106]. For instance, Cheng et al. prepared 3D bio-printed Alg-Gel composites, which promoted

Table 1
Characteristics of modified gelatin and natural polymers composite for BTE.

Natural Polymers	Advantages of single material	Disadvantages of single material	Characteristics of composite materials	Ref.
CS	Biocompatibility; biodegradability; antibacterial properties.	Stability; mechanical strength; osteoinductivity.	Improved mechanical strength; osteoconductivity; significant biomineralization effect; and enhanced cell adhesion.	[108]
SF	Good biocompatibility, good mechanical strength; and high thermal stability.	Slow biodegradation, high fragility; and presence of residual contaminants.	Good biodegradability; flexibility; tensile strength and mechanical properties.	[109]
Alg	Good biocompatibility; simple gelation and easy functionalization.	Poor mechanical properties; uncontrolled degradation; and hard to sterilize.	Improved mechanical properties; regular pore structure; good biodegradability; and beneficial to cell growth.	[110]
Hyaluronic acid (HA)	Good biocompatibility, biodegradability; good viscoelasticity and easy functionalization.	Poor mechanical properties; difficult to process by electrostatic spinning.	Good biocompatibility, biodegradability and mechanical strength; strong cell adhesion is conducive to osteoblast growth.	[111]
Cellulose	Good biocompatibility and easy to functionalize.	Poor mechanical properties and slow biodegradation.	Good mechanical strength; proper porosity; and strong cell adhesion.	[112]
Fucoidan	Good biocompatibility, osteoinductivity; easy functionalization; easy gelation.	Slow degradation and poor mechanical properties.	Good antibacterial activity; antioxidant; cytocompatibility and hemostatic properties.	[113]

the expression of osteogenic genes and proteins. The mechanical strength of the scaffold was similar to that of mouse dermal tissue structure with a more regular pore structure [107]. The advantages and disadvantages of common single natural polymers for bone repair and the material properties of the compounds with gelatin are summarized in Table 1.

4.1.2. Synthetic polymer

Synthetic polymers are formed by the polymerization of repeating monomers. Through designing the polymer functional groups and molecular weights appropriately, synthetic polymers exhibit specific structures and properties, such as controlled products and suitable mechanical properties. However, compared to natural polymers, synthetic polymers are usually poorer in degradability. The modification of gelatin with synthetic polymer materials not only compensates for the weak mechanical properties of gelatin, but also can prepare scaffold materials with adjustable properties according to the growth characteristics of bone cells. The major bone regeneration synthetic polymer scaffolds, such as PCL, PLA, poly (lactic-*co*-glycolic acid) (PLGA), and HAp are used for gelatin modification.

PCL is made by ring-opening polymerization of ε-caprolactone, which is a non-toxic, biodegradable polyester with certain rigidity and strength. However, its degradation rate is slow, and the hydrophobicity of PCL is not conducive to cell adhesion and proliferation [114]. For instance, Yuan et al. prepared a series of composite fiber membranes with different ratios of PCL and gelatin by electrospinning, which showed that a higher PCL content was beneficial to maintain the fiber structure of electrospun membranes, while a higher gelatin content could effectively improve the degradation rate of the scaffolds [115]. In addition, Liu et al. prepared modified gelatin scaffolds with different degradation rates according to the different degradation rates of PCL and gelatin, showed that the composite scaffold material could increase the adhesion of osteoblasts to bone and could effectively promote the regeneration of alveolar bone [116].

PLA is composed of polymerized lactic acid monomers that possess several essential characteristics for bone regeneration, such as cytocompatibility, thermal stability, and non-toxic degradation products [117,118]. For example, Yu et al. designed bioactive resveratrol PLA-Gel porous nanofiber scaffolds with good properties by electrostatic spinning technique, which had effective in cartilage injury repair [119].

PLGA is a random polymerization of lactic acid and hydroxyacetic acid monomers with good biocompatibility and biodegradability [120,121]. PLGA is the most widely used synthetic polymer for bone regeneration applications. Besides, the degradation rate of PLGA is able to be regulated from weeks to months by simply changing the ratio of the two monomers [122,123]. For instance, Li et al. prepared an injectable PLGA-Gel hydrogel scaffold loaded with simvastatin for enhancing osteogenic healing of alveolar bone. The composite hydrogel scaffold was shown to have excellent mobility at 37 °C with improved degradation rate and sustained osteogenic effect on the regeneration of new bone cells [124]. The advantages and disadvantages of other synthetic polymer materials for bone repair as well as the characteristics of composites with gelatin are summarized in Table 2.

4.2. Inorganic materials

Inorganic materials used for bone repair mainly include bioceramics, metallic materials and other inorganic materials, which usually have excellent mechanical properties and osteoinductive activity to compensate for the shortcomings of natural gelatin [132, 133]. The following mainly introduced the common inorganic materials composited with gelatin such as HAp, bioactive glasses (BGs), silver nanoparticles (AgNPs) and black phosphorus (BP) nanosheets [134–136]. The advantages and disadvantages of other common inorganic materials for bone repair applications and the properties of gelatin composites are summarized in Table 3.

HAp is a material with high similarity to the mineral composition of bone and is an attractive source of artificial bone material for BTE, with good compressive strength, biocompatibility and corrosion resistance [148]. It is commonly used as a replacement material for teeth and skeletons. The porous structure of HAp is beneficial as a bone scaffold to support cartilage repair and osteogenic regeneration. However, single HAp is brittle, poorly stiffened, slowly degraded, and has poor adhesion to cells. While composites of HAp with gelatin are beneficial for cell adhesion and growth, which can also improve its biodegradability and stability [149]. For example, Zhu et al. used glutaraldehyde as a cross-linking agent to synthesize porous Gel-HAp scaffold materials with different

Table 2
Characteristics of modified gelatin and synthetic polymers composite for BTE.

Synthetic Polymers	Advantages of single material	Disadvantages of single material	Characteristics of composite materials	Ref.
Polyglycolic acid	Controllable degradation rat; osteoinductivity.	Poor Biocompatibility; adhesion.	Mechanical strength; osteoinductivity; biomineralization effect.	[125]
Polyethylene glycol (diol) diacrylate	Flexibility; modifiable;	Adhesion; fragile.	Mechanical enhancement good biodegradability; flexibility.	[126]
Ethyl phthalate	Good plasticity; good mechanical strength; and high thermal stability	Uncontrolled degradation.	Improved mechanical properties, regular pore structure; Shape control.	[127]
N-allylglycine	Controllable mechanical properties; good plasticity; Good thermal stability.	Poor biocompatibility; osteoinductivity.	Controllable degradation and mechanical strength.	[128]
Poly (vinyl alcohol)	Mechanical strength and plasticity.	Poor degradation and biocompatibility.	Good biocompatibility mechanical strength; and degradation.	[129]
Polyorthoesters	Mechanical strength; plasticity; biocompatibility; stabilization.	Degradation; osteoinductivity.	Biocompatibility; mechanical strength.	[130, 131]

Table 3
Characteristics of modified gelatin and inorganic materials composite for BTE.

Inorganic materials	Advantages of single material	Disadvantages of single material	Characteristics of composite materials	Ref.
Calcium octaphosphate	Oteoinductivity; mechanical strength and biocompatibility.	Low solubility; slow degradation.	High rate of osteogenesis; mechanical enhancement.	[137]
Graphene oxide	Mechanical strength; high optical transparency; electrical conductivity;	Slow degradation and low swelling rate	Excellent osteogenic effect and mechanical strength.	[138]
Hydrotalcite	Excellent adsorbability; adjustable structure; antimicrobial activity.	Poor dispersion; biocompatibility; mechanical strength.	Anti-infection; plasticity; biocompatibility; Osteogenic induction	[139,140]
AuNPs	Antimicrobial activity; mechanical strength; osteoinductivity.	Poor dispersion; slow degradation.	Anti-infection; Osteogenic; Adjustable performance; mechanical strength.	[141,142]
Calcium sulfate	Tolerance; osteoinductivity; plasticity	Poor anti-infection; hyperbiodegradation.	Osteoinductivity Excellent biodegradability	[143–145]
Carbon nanotubes	Excellent toughness; electroconductibility; high specific surface area.	Biocompatibility.	Osteogenic induction; Biocompatibility; excellent biodegradability.	[146,147]

concentrations, which could effectively support, cell adhesion and proliferation [72]. What's more, Conrad et al. made a modified gelatin bone scaffold material by incorporating nano-HAp into gelatin-based micro-ribbon hydrogel, which was able to rapidly induce endogenous cranial bone regeneration with increased osteoclast activity [150].

BGs are silicate glasses composed of basic components such as Na_2O, SiO_2, CaO and P_2O_5. Bioactive glass will slowly release soluble Si、P、Na and Ca ions when in contact with body fluids, which is conducive to promoting bone repair and angiogenesis [151]. In addition, Ce、Mg、Zn、Fe、Sr、Ag、B and other beneficial elements for bone repair can be added to the preparation of bioactive glass. For example, Mostajeran et al. prepared SA-Gel-BG/Ce scaffolds by compositing cerium-doped bioactive glass with SA/gelatin, which showed a significant increase in the mechanical properties and showed outstanding anti-inflammatory, antimicrobial, osteogenic as well as angiogenic properties [152,153].

Bacterial infections during bone injury impair the healing and repairing ability of bone tissues. The high use of antibiotics in the clinic may lead to bacterial resistance, while the unique antibacterial mechanism of AgNPs is almost non-resistant to bacteria and has a wide range of antibacterial properties [154]. In addition, AgNPs have photothermal conversion ability, which enhances the antibacterial performance and osteoinductive activity, and the composite with gelatin can improve the mechanical properties of composite scaffolds [116]. For example, Ou et al. composited nanosilver (nAg), halloysite nanotubes (HNTs) with GelMA to prepare nAg/HNTs/GelMA composite hydrogels. The addition of nAg not only improved the mechanical and antimicrobial properties of the composite hydrogel, but also regulated the macrophage inflammatory reaction and accelerated bone regeneration.

BP nanosheets, as a novel two-dimensional nanomaterial, have been widely studied in BTE due to the special physicochemical properties, such as excellent electrical conductivity, photothermal conversion ability and excellent biodegradability [155]. Moreover, in physiological environment, the degradation products of black phosphorus nanosheets are phosphates, which contribute to bone tissue mineralization. For instance, Jing et al. incorporated magnesium-modified BP into GelMA to prepare a photosensitive and conductive composite hydrogel, which exhibited effective antimicrobial properties under near-infrared irradiation and induced nerve fiber regeneration to promote bone repair [156].

In summary, Gelatin had the ability to be compounded with a variety of other bioactive materials in order to prepare gelatin composite scaffolds with excellent performance, which could be used to meet different types of bone defects. In addition, bone defects in different pathologic states are also worthy of attention, such as postmenopausal osteoporosis and diabetic osteoporosis patients. Gelatin composite scaffolds effectively promoted the adhesion and proliferation of osteoblasts, which was contributed to alleviate the pathological conditions of bone microstructure degradation and bone mineral density loss in postmenopausal osteoporosis patients [157]. Moreover, gelatin scaffold materials were capable of loading active molecules, such as BMP-2, estrogen and other active molecules, which accelerated the regeneration process of the bone microenvironment [158]. For the treatment of patients with diabetic osteoporosis, gelatin scaffolds loaded with anti-inflammatory active molecules or osteogenesis-related growth factors were used to improve osteoblast proliferation and differentiation and metabolic processes [159]. At present, although there is no clear case of gelatin scaffolds in the research of clinical treatment, it can be found that modified gelatin scaffolds show great potential in preclinical treatment in the field of tissue engineering and regenerative medicine from the current research. In particular, gelatin and hyaluronic acid/hydroxyapatite composite scaffold materials have been widely used in preclinical studies of cartilage regeneration and wound healing [160].

5. Summary and prospect

Gelatin, a natural hydrophilic polymer, has excellent biocompatibility, biodegradability, and superior biological properties in the field of bone tissue engineering. To compensate for the insufficient mechanical properties of gelatin, researchers have modified gelatin or compounded it with other various natural or synthetic polymeric materials, as well as bioactive ceramics and inorganic metal/non-metal materials to obtain more superior performance of bone tissue engineering scaffold materials. Although the clinical practice research on gelatin-based composite scaffold materials in the field of bone tissue regeneration is still in its infancy, mainly focusing on preclinical studies such as in vitro cell experiments, mechanical property tests, and animal experiments, this field is undergoing rapid development. With the continuous emergence and maturity of advanced technologies such as electrospinning, additive manufacturing, 3D printing, 4D printing, and bone organoids, scientists have been able to customize biological scaffolds with high biocompatibility and excellent matching to the shape of bone defects. These meticulously developed scaffold materials aim to produce bone tissue repair materials with higher degrees of matching and functionality for more effective treatment of bone tissue injuries. Therefore, gelatin-based composite scaffold materials are gradually becoming one of the most promising scaffold materials in the field of bone tissue regeneration [161,162].

Data availability statement

The authors declare that no data associated with our study has been deposited into a publicly available repository since no data was used for the research described in the article.

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Ethics declarations

Review and/or approval by an ethics committee was not needed for this study because it don't include any human or animal participation.

Consent to publish

All authors agree to the submission and publication of the manuscript.

CRediT authorship contribution statement

Enguang Wu: Writing – review & editing, Writing – original draft, Conceptualization. **Lianghui Huang:** Writing – review & editing, Conceptualization. **Yao Shen:** Supervision. **Zongyi Wei:** Methodology. **Yangbiao Li:** Methodology. **Jin Wang:** Validation, Investigation, Funding acquisition, Formal analysis, Data curation. **Zhenhua Chen:** Validation, Supervision, Investigation, Funding acquisition, Formal analysis, Data curation.

Declaration of competing interest

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

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Not applicable.

Abbreviations

AgNPs	Silver nanoparticles
Alg	Alginate
BGs	Bioactive glasses
BP	Nanosheets black phosphorus nanosheets
BTE	Bone tissue engineering
CS	Chitosan
EGCG	Epigallocatechin gallate
Gly	Glycine
Gel	Gelatin
HAp	Hydroxyapatite
HUVECs	Human umbilical vein endothelial cells
Hyp	Hydroxyproline
MSCs	Mesenchymal stem cells
PCL	Polycaprolactone
PLA	Polylactic acid
PLGA	Poly (lactic-*co*-glycolic acid)
Pro	Proline
PVA	Polyvinyl Alcohol
SF	Silk fibroin
3D	Three-dimensional
4D	Four-dimensional

References

[1] L.F.B. Nogueira, B.C. Maniglia, R. Buchet, J.L. Millán, P. Ciancaglini, M. Bottini, A.P. Ramos, Three-dimensional cell-laden collagen scaffolds: from biochemistry to bone bioengineering, J. Biomed. Mater. Res. B 110 (2022) 967–983.

[2] X. Zhou, Z. Wang, T. Li, Z. Liu, X. Sun, W. Wang, L. Chen, C. He, Enhanced tissue infiltration and bone regeneration through spatiotemporal delivery of bioactive factors from polyelectrolytes modified biomimetic scaffold, Mater Today Bio 20 (2023) 100681.

[3] Y. Yang, M. Wang, S. Yang, Y. Lin, Q. Zhou, H. Li, T. Tang, Bioprinting of an osteocyte network for biomimetic mineralization, Biofabrication 12 (2020) 045013.
[4] C. Çiçek, G. Filinte, K. Basak, A.F. Kayis, Artificial dermis and human recombinant epidermal growth factor application for the management of critical size calvarial defect, J. Craniofac. Surg. 35 (2024) 993–998.
[5] B.J. Sun, Y.J. Sun, S.W. Han, R.T. Zhang, X.J. Wang, C.X. Meng, T. Ji, C.H. Sun, N. Ren, S.H. Ge, H. Liu, Y. Yu, J.A. Wang, Electroactive hydroxyapatite/carbon nanofiber scaffolds for osteogenic differentiation of human adipose-derived stem cells, Int. J. Mol. Sci. 24 (2023) 530.
[6] Y. Liu, L.X. He, L.J. Cheng, X.S. Li, M. Gao, Q.Z. Li, J.J. Gao, M. Ramalingam, Enhancing bone grafting outcomes: a comprehensive review of antibacterial artificial composite bone scaffolds, Med Sci Monitor 29 (2023) e939972.
[7] S.Y. Shen, R. Liu, C.H. Song, T. Shen, Y.W. Zhou, J.X. Guo, B. Kong, Q. Jiang, Fish scale-derived scaffolds with MSCs loading for photothermal therapy of bone defect, Nano Res. 16 (2023) 7383–7392.
[8] J.Z. Zhang, S.G. Li, H.Y. He, L. Han, S.M. Zhang, L. Yang, W.X. Han, X.W. Wang, J. Gao, J.W. Zhao, W.D. Shi, Z. Wu, H. Wang, Z.C. Zhang, L.C. Zhang, W. Chen, Q.T. Zhu, T.S. Sun, P.F. Tang, Y.Z. Zhang, Clinical guidelines for indications, techniques, and complications of autogenous bone grafting, Chinese Med J-Peking 137 (2024) 5–7.
[9] J.X. Ye, N.Y. Liu, Z.X. Li, L.H. Liu, M. Zheng, X.P. Wen, N. Wang, Y.Q. Xu, B.M. Sun, Q. Zhou, Injectable, hierarchically degraded bioactive scaffold for bone regeneration, Acs Appl Mater & Interfaces 15 (2023) 11458–11473.
[10] Y. Ren, C.R. Zhang, Y.H. Liu, W.Q. Kong, X. Yang, H.Y. Niu, L. Qiang, H. Yang, F. Yang, C.W. Wang, J.W. Wang, Advances in 3D printing of highly bioadaptive bone tissue engineering scaffolds, Acs Biomater Sci Eng 10 (2023) 255–270.
[11] S. Saurav, P. Sharma, A. Kumar, Z. Tabassum, M. Girdhar, N. Mamidi, A. Mohan, Harnessing natural polymers for nano-scaffolds in bone tissue engineering: a comprehensive overview of bone disease treatment, Curr. Issues Mol. Biol. 46 (2024) 585–611.
[12] C. Xu, Z.Z. Liu, X. Chen, Y. Gao, W.J. Wang, X.J. Zhuang, H. Zhang, X.F. Dong, Bone tissue engineering scaffold materials: fundamentals, advances, and challenges, Chinese Chem Lett 35 (2024) 109197.
[13] S.F. Darghiasi, A. Farazin, H.S. Ghazali, Design of bone scaffolds with calcium phosphate and its derivatives by 3D printing: a review, J Mech Behav Biomed 151 (2024) 106391.
[14] A.K. Sri, C. Arthi, N.R. Neya, G.S. Hikku, Nano-hydroxyapatite/collagen composite as scaffold material for bone regeneration, Biomed Mater 18 (2023) 032002.
[15] L. Fan, Y.R. Ren, S. Emmert, I. Vuckovic, S. Stojanovic, S. Najman, R. Schnettler, M. Barbeck, K. Schenke-Layland, X. Xiong, The use of collagen-based materials in bone tissue engineering, Int. J. Mol. Sci. 24 (2023) 3744.
[16] X.Y. Zhai, Y.Q. Wu, H.P. Tan, Gelatin-based targeted delivery systems for tissue engineering, Curr. Drug Targets 24 (2023) 673–687.
[17] C. Wang, Z. Ma, K. Yuan, T. Ji, Using scaffolds as drug delivery systems to treat bone tumor, Nanotechnology 33 (2022) 212002.
[18] H.R. El-Seedi, N.S. Said, N. Yosri, H.B. Hawash, D.M. El-Sherif, M. Abouzid, M.M. Abdel-Daim, M. Yaseen, H. Omar, Q.Y. Shou, N.F. Attia, X.B. Zou, Z.M. Guo, S.A.M. Khalifa, Gelatin nanofibers: recent insights in synthesis, bio-medical applications and limitations, Heliyon 9 (2023) e16228.
[19] L.Q. Sun, M.M. Liu, Y.Q. Li, S.H. Zhang, T.H. Zhu, J. Du, A.U.R. Khan, Biomimetic short fiber reinforced 3-dimensional scaffold for bone tissue regeneration, Biomed Mater 19 (2024) 025030.
[20] C.L. Wang, J.L. Dong, F.X. Liu, N. Liu, L.X. Li, 3D-printed PCL@BG scaffold integrated with SDF-1α-loaded hydrogel for enhancing local treatment of bone defects, J. Biol. Eng. 18 (2024) 1.
[21] N. Mamidi, F. Ijadi, M.H. Norahan, Leveraging the recent advancements in GelMA scaffolds for bone tissue engineering: an assessment of challenges and opportunities, Biomacromolecules 25 (2023) 2075–2113.
[22] K. Guillén-Carvajal, B. Valdez-Salas, E. Beltrán-Partida, J. Salomón-Carlos, N.L. Cheng, Chitosan, gelatin, and collagen hydrogels for bone regeneration, Polymers 15 (2023) 2762.
[23] Y.P. Singh, S. Dasgupta, Gelatin-based electrospun and lyophilized scaffolds with nano scale feature for bone tissue engineering application: review, J. Biomater. Sci. Polym. Ed. 33 (2022) 1704–1758.
[24] M. Prasathkumar, S. Sadhasivam, Chitosan/hyaluronic acid/alginate and an assorted polymers loaded with honey, plant, and marine compounds for progressive wound healing-know-how, Int. J. Biol. Macromol. 186 (2021) 656–685.
[25] B. Zhu, Y. Liu, Y.L. Zhao, X.Y. Dou, L.B. Wang, S.Y. Min, X.G. Liu, D. Qiu, A pH-neutral bioactive glass empowered gelatin-chitosan-sodium phytate composite scaffold for skull defect repair, J. Mater. Chem. B 11 (2023) 9742–9756.
[26] T.T. Xu, S.P. Huang, Y.L. Min, Q.J. Xu, Gelatin network reinforced poly (vinylene carbonate-acrylonitrile) based composite solid electrolyte for all-solid-state lithium metal batteries, Chem Eng J 475 (2023) 146409.
[27] L. Lin, J.M. Regenstein, S. Lv, J.F. Lu, S.T. Jiang, An overview of gelatin derived from aquatic animals: properties and modification, Trends Food Sci Tech 68 (2017) 102–112.
[28] W. Wu, C. Shi, Y. Zi, H. Gong, L. Chen, G. Kan, X. Wang, J. Zhong, Effects of polyphenol and gelatin types on the physicochemical properties and emulsion stabilization of polyphenol-crosslinked gelatin conjugates, Food Chem. X 22 (2024) 101250.
[29] D.S. Kolotova, E.V. Borovinskaya, V.V. Bordiyan, Y.F. Zuev, V.V. Salnikov, O.S. Zueva, S.R. Derkach, Phase behavior of aqueous mixtures of sodium alginate with fish gelatin: effects of pH and ionic strength, Polymers 15 (2023) 2253.
[30] M.I. Ahmad, Y.H. Li, J.F. Pan, F. Liu, H.J. Dai, Y. Fu, T. Huang, S. Farooq, H. Zhang, Collagen and gelatin: structure, properties, and applications in food industry, Int. J. Biol. Macromol. 254 (2024) 128037.
[31] A. Veis, J. Cohen, Reversible transformation of gelatin to the collagen structure, Nature 186 (1960) 720–721.
[32] B. Lv, L. Lu, L.C. Hu, P. Cheng, Y.Q. Hu, X.D. Xie, G.D. Dai, B.B. Mi, X. Liu, G.H. Liu, Recent advances in gelma hydrogel transplantation for musculoskeletal disorders and related disease treatment, Theranostics 13 (2023) 2015–2039.
[33] E.S. Abar, S. Vandghanooni, A. Torab, M. Jaymand, M. Eskandani, A comprehensive review on nanocomposite biomaterials based on gelatin for bone tissue engineering, Int. J. Biol. Macromol. 254 (2024) 127556.
[34] G. Battogtokh, Y. Joo, S.M. Abuzar, H. Park, S.J. Hwang, Gelatin coating for the improvement of stability and cell uptake of hydrophobic drug-containing liposomes, Molecules 27 (2022) 1041.
[35] K. Tarnutzer, D. Siva Sankar, J. Dengjel, C.Y. Ewald, Collagen constitutes about 12% in females and 17% in males of the total protein in mice, Sci. Rep. 13 (2023) 4490.
[36] C.D. Zhen, Y.B. Shi, W.G. Wang, G.Z. Zhou, H. Li, G.M. Lin, F. Wang, B.T. Tang, X.L. Li, Advancements in gradient bone scaffolds: enhancing bone regeneration in the treatment of various bone disorders, Biofabrication 16 (2024) 032004.
[37] M. Janmohammadi, Z. Nazemi, A.O.M. Salehi, A. Seyfoori, J. John, M.S. Nourbakhsh, M. Akbari, Cellulose-based composite scaffolds for bone tissue engineering and localized drug delivery, Bioact. Mater. 20 (2023) 137–163.
[38] M. Tortorici, A. Petersen, G.N. Duda, S. Checa, The degradation of synthetic polymeric scaffolds with strut-like architecture influences the mechanics-dependent repair process of an osteochondral defect in silico, Front Bioeng Biotech 10 (2022) 846665.
[39] S. Tariq, S.A. Shah, F. Hameed, Z. Mutahir, H. Khalid, A. Tufail, H. Akhtar, A.A. Chaudhry, A.F. Khan, Tissue engineered periosteum: fabrication of a gelatin basedtrilayer composite scaffold with biomimetic properties for enhanced bone healing, Int. J. Biol. Macromol. 263 (2024) 130371.
[40] T. Hatakeyama, R. Hamai, Y. Shiwaku, T. Anada, S. Sakai, T. Sato, K. Baba, K. Sasaki, O. Suzuki, Effects of degradation products from gelatin spongy scaffolds on angio-osteogenic capacity, Sci Technol Adv Mat 24 (2023) 2277675.
[41] J. Han, J.Z. Wu, X.J. Xiang, L.X. Xie, R.G. Chen, L. Li, K. Ma, Q. Sun, R.H. Yang, T.L. Huang, L.P. Tong, L. Zhu, H.Y. Wang, C.E. Wen, Y. Zhao, J.F. Wang, Biodegradable BBG/PCL composite scaffolds fabricated by selective laser sintering for directed regeneration of critical-sized bone defects, Mater Design 225 (2023) 111543.
[42] M. Ebrahimi, Porosity parameters in biomaterial science: definition, impact, and challenges in tissue engineering, Front. Mater. Sci. 15 (2021) 352–373.

[43] C. Xu, H.Y. Zhang, S.N. Yu, W.Z. Wu, L. Zhang, Q.P. Liu, L.Q. Ren, Direct ink writing of porous Fe scaffolds for bone implants: pore size evolution and effect on degradation and mechanical properties, J. Mater. Res. Technol. 25 (2023) 4901–4912.
[44] W. Prananingrum, Y. Naito, S. Galli, J. Bae, K. Sekine, K. Hamada, Y. Tomotake, A. Wennerberg, R. Jimbo, T. Ichikawa, Bone ingrowth of various porous titanium scaffolds produced by a moldless and space holder technique: an in vivo study in rabbits, Biomed Mater 11 (2016) 015012.
[45] H.X. Zhao, L.H. Li, S. Ding, C.X. Liu, J.Y. Ai, Effect of porous structure and pore size on mechanical strength of 3D-printed comby scaffolds, Mater. Lett. 223 (2018) 21–24.
[46] N.R. El-Bahrawy, H. Elgharbawy, A. Elmekawy, M. Salem, R. Morsy, Development of porous Hydroxyapatite/PVA/Gelatin/Alginate hybrid flexible scaffolds with improved mechanical properties for bone tissue engineering, Mater. Chem. Phys. 319 (2024) 129332.
[47] S.L. Zhu, B.J. Zhao, M.C. Li, H. Wang, J.Y. Zhu, Q.T. Li, H.C. Gao, Q. Feng, X.D. Cao, Microenvironment responsive nanocomposite hydrogel with NIR photothermal therapy, vascularization and anti-inflammation for diabetic infected wound healing, Bioact. Mater. 26 (2023) 306–320.
[48] C.E. Ayres, B.S. Jha, S.A. Sell, G.L. Bowlin, D.G. Simpson, Nanotechnology in the Design of Soft Tissue Scaffolds: Innovations in Structure and Function, vol. 2, Wiley Nanomed Nanobi, 2010, pp. 20–34.
[49] H.V. Almeida, B.N. Sathy, I. Dudurych, C.T. Buckley, F.J. O'Brien, D.J. Kelly, Anisotropic shape-memory alginate scaffolds functionalized with either type I or type II collagen for cartilage tissue engineering, Tissue Eng Pt A 23 (2017) 55–68.
[50] A. Mohammed, A. Jiménez, P. Bidare, A. Elshaer, A. Memic, H. Hassanin, K. Essa, Review on engineering of bone scaffolds using conventional and additive manufacturing technologies, 3D Print. Addit. Manuf. (2023) 2329–7662.
[51] Y.T. Zhang, D. Wu, X. Zhao, M. Pakvasa, A.B. Tucker, H.X. Luo, K.H. Qin, D.A. Hu, E.J. Wang, A.J. Li, M. Zhang, Y.K. Mao, M. Sabharwal, F. He, C.C. Niu, H. Wang, L.J. Huang, D.Y. Shi, Q. Liu, N. Ni, K. Fu, C.N. Chen, W. Wagstaff, R.R. Reid, A. Athiviraham, S.R. Ho, M.J. Lee, K. Hynes, J. Strelzow, T.C. He, M. El Dafrawy, Stem cell-friendly scaffold biomaterials: applications for bone tissue engineering and regenerative medicine, Front Bioeng Biotech 8 (2020) 598607.
[52] J.X. Chen, Y.H. Jing, Y.H. Liu, Y.X. Luo, Y.T. He, X.Z. Qiu, Q.B. Zhang, H.Y. Xu, Molecularly imprinted macroporous hydrogel promotes bone regeneration via osteogenic induction and osteoclastic inhibition, Adv Healthc Mater (2024) e2400897.
[53] Y.N. Gou, Y.R. Huang, W.P. Luo, Y.N. Li, P. Zhao, J.M. Zhong, X.Y. Dong, M.C. Guo, A.H. Li, A.L. Hao, G.Z. Zhao, Y.H. Wang, Y. Zhu, H. Zhang, Y.H. Shi, W. Wagstaff, H.H. Luu, L.L. Shi, R.R. Reid, T.C. He, J.M. Fan, Adipose-derived mesenchymal stem cells (MSCs) are a superior cell source for bone tissue engineering, Bioact. Mater. 34 (2024) 51–63.
[54] A. Ho-Shui-Ling, J. Bolander, L.E. Rustom, A.W. Johnson, F.P. Luyten, C. Picart, Bone regeneration strategies: engineered scaffolds, bioactive molecules and stem cells current stage and future perspectives, Biomaterials 180 (2018) 143–162.
[55] H.B. Li, R.J. Zhou, Q. Shu, M.J. Xie, Y. He, Precise Printing of Microfiber Scaffold with Gelatin Methacryloyl (GelMA)/polyethylene Oxide (PEO) Bioink, Bioengineering-Basel, vol. 10, 2023, p. 130.
[56] L. Chen, G.W. Huang, M. Yu, Y. Liu, T. Cheng, A.G. Li, W. Wang, S.N. Qin, Recent progress on 3D-printed gelatin methacrylate-based biomaterials for articular cartilage repair, Int J Bioprinting 9 (2023) 239–256.
[57] S. Han, K. Nie, J. Li, Q. Sun, X. Wang, X. Li, Q. Li, 3D electrospun nanofiber-based scaffolds: from preparations and properties to tissue regeneration applications, Stem Cells Int. 2021 (2021) 8790143.
[58] H. Samadian, H. Khastar, A. Ehterami, M. Salehi, Bioengineered 3D nanocomposite based on gold nanoparticles and gelatin nanofibers for bone regeneration: in vitro and in vivo study, Sci. Rep. 11 (2021) 13877.
[59] J. Chakraborty, J. Fernández-Pérez, K.A. van Kampen, S. Roy, T. Ten Brink, C. Mota, S. Ghosh, L. Moroni, Development of a biomimetic arch-like 3D bioprinted construct for cartilage regeneration using gelatin methacryloyl and silk fibroin-gelatin bioinks, Biofabrication 15 (2023) 035009.
[60] H.R. El-Seedi, N.S. Said, N. Yosri, H.B. Hawash, D.M. El-Sherif, M. Abouzid, M.M. Abdel-Daim, M. Yaseen, H. Omar, Q. Shou, N.F. Attia, X. Zou, Z. Guo, S.A. M. Khalifa, Gelatin nanofibers: recent insights in synthesis, bio-medical applications and limitations, Heliyon 9 (2023) e16228.
[61] R. Wu, Y. Li, M. Shen, X. Yang, L. Zhang, X. Ke, G. Yang, C. Gao, Z. Gou, S. Xu, Bone tissue regeneration: the role of finely tuned pore architecture of bioactive scaffolds before clinical translation, Bioact. Mater. 6 (2021) 1242–1254.
[62] T. Al Kayal, P. Losi, S. Pierozzi, G. Soldani, A new method for fibrin-based electrospun/sprayed scaffold fabrication, Sci. Rep. 10 (2020) 5111.
[63] P.K. Chakraborty, J. Adhikari, P. Saha, Facile fabrication of electrospun regenerated cellulose nanofiber scaffold for potential bone-tissue engineering application, Int. J. Biol. Macromol. 122 (2019) 644–652.
[64] H.Z. Xu, S. Yagi, S. Ashour, L. Du, M.E. Hoque, L. Tan, A review on current nanofiber technologies: electrospinning, centrifugal spinning, and electro-centrifugal spinning, Macromol. Mater. Eng. 308 (2023) 2200502.
[65] E.L. Gill, W.Y. Wang, R.S. Liu, Y.Y.S. Huang, Additive batch electrospinning patterning of tethered gelatin hydrogel fibres with swelling-induced fibre curling, Addit. Manuf. 36 (2020) 101456.
[66] S. Gautam, C. Sharma, S.D. Purohit, H. Singh, A.K. Dinda, P.D. Potdar, C.F. Chou, N.C. Mishra, Gelatin-polycaprolactone-nanohydroxyapatite electrospun nanocomposite scaffold for bone tissue engineering, Mater Sci Eng C Mater Biol Appl. 119 (2021) 111588.
[67] Y. Yang, L. Xu, J. Wang, Q. Meng, S. Zhong, Y. Gao, X. Cui, Recent advances in polysaccharide-based self-healing hydrogels for biomedical applications, Carbohydr. Polym. 283 (2022) 119161.
[68] S. Norris, S. Delgado, A. Kasko, Mechanically robust photodegradable gelatin hydrogels for 3D cell culture and in situ mechanical modification, Abstr. Pap. Am. Chem. Soc. 256 (2018).
[69] D.H. Lee, A. Tamura, Y. Arisaka, J.H. Seo, N. Yui, Mechanically reinforced gelatin hydrogels by introducing slidable supramolecular cross-linkers, Polymers 11 (2019) 1787.
[70] M.H. Abu Elella, N. Aamer, Y.M.A. Mohamed, H.A. El Nazer, R.R. Mohamed, High-potential removal of copper (II) ions from aqueous solution using antimicrobial crosslinked grafted gelatin hydrogels, J. Polym. Environ. 31 (2023) 1071–1089.
[71] L.N. Wang, H.J. Zhang, X.Q. Liu, Y. Liu, X. Zhu, X.H. Liu, X.Y. You, A physically cross-linked sodium alginate-gelatin hydrogel with high mechanical strength, ACS Appl. Polym. Mater. 3 (2021) 3197–3205.
[72] Y.H. Zhu, S. Chen, C.F. Zhang, T. Ikoma, H.M. Guo, X.Y. Zhang, X.N. Li, W.Y. Chen, Novel microsphere-packing synthesis, microstructure, formation mechanism and in vitro biocompatibility of porous gelatin/hydroxyapatite microsphere scaffolds, Ceram. Int. 47 (2021) 32187–32194.
[73] P. Le Thi, Y. Lee, D.H. Nguyen, K.D. Park, In situ forming gelatin hydrogels by dual-enzymatic cross-linking for enhanced tissue adhesiveness, J. Mater. Chem. B 5 (2017) 757–764.
[74] S. Bose, C.M. Phan, M. Rizwan, J.W. Tse, E. Yim, L. Jones, R. Pignatello, H. Almeida, D. Santonocito, C. Puglia, Fabrication and characterization of an enzyme-triggered, therapeutic-releasing hydrogel bandage contact lens material, Pharmaceutics 16 (2024) 26.
[75] Y. Tu, N. Chen, C. Li, H. Liu, R. Zhu, S. Chen, Q. Xiao, J. Liu, S. Ramakrishna, L. He, Advances in injectable self-healing biomedical hydrogels, Acta Biomater. 90 (2019) 1–20.
[76] C. Wei, W. Shi, C. Zhao, S. Yang, J. Zheng, J. Zhong, T. Zhao, S. Kong, X. Gong, M. Liu, Superwetting injectable hydrogel with ultrastrong and fast tissue adhesion for minimally invasive hemostasis, Adv Healthc Mater 12 (2023) e2201799.
[77] Z. Shi, Q. Zhong, Y. Chen, J. Gao, X. Pan, Q. Lian, R. Chen, P. Wang, J. Wang, Z. Shi, H. Cheng, Nanohydroxyapatite, nanosilicate-reinforced injectable, and biomimetic gelatin-methacryloyl hydrogel for bone tissue engineering, Int J Nanomedicine 16 (2021) 5603–5619.
[78] M. Mahmoudi Saber, Strategies for surface modification of gelatin-based nanoparticles, Colloid Surface B. 183 (2019) 110407.
[79] S. Schrade, L. Ritschl, R. Süss, P. Schilling, M. Seidenstuecker, Gelatin nanoparticles for targeted dual drug release out of alginate-di-aldehyde-gelatin Gels, Gels 8 (2022) 365.
[80] M. Kalogeropoulou, P.J. Díaz-Payno, M.J. Mirzaali, G. van Osch, L.E. Fratila-Apachitei, A.A. Zadpoor, 4D printed shape-shifting biomaterials for tissue engineering and regenerative medicine applications, Biofabrication 16 (2024) 022002.
[81] M.P. Ferraz, An overview on the big players in bone tissue engineering: biomaterials, scaffolds and cells, Int. J. Mol. Sci. 25 (2024) 3836.
[82] X. Chen, S.Y. Han, W.H. Wu, Z.H. Wu, Y. Yuan, J. Wu, C.S. Liu, Harnessing 4D printing bioscaffolds for advanced orthopedics, Small 18 (2022) e2106824.

[83] Y.Y. Li, J.Q. You, H.X. Lv, C. Wang, S.B. Zhai, S.C. Ren, X.Y. Liu, Y.D. Zhang, Y.M. Zhou, 4D-printed dual-responsive bioscaffolds for treating critical-sized irregular bone defects, Chem Eng J 489 (2024) 151205.
[84] J. Chakraborty, J. Fernández-Pérez, M.T. Ghahfarokhi, K.A. van Kampen, T.T. Brink, J. Ramis, M. Kalogeropoulou, R. Cabassi, C.D. Fernández, F. Albertini, C. Mota, S. Ghosh, L. Moroni, Development of 4D-bioprinted shape-morphing magnetic constructs for cartilage regeneration using a silk fibroin-gelatin bioink, Cell Reports Physical Science 5 (2024) 101819.
[85] S.L. Wu, X.M. Wu, X.H. Wang, J.C. Su, Hydrogels for bone organoid construction: from a materiobiological perspective, J. Mater. Sci. Technol. 136 (2023) 21–31.
[86] J. Wang, Y. Wu, G.F. Li, F.J. Zhou, X. Wu, M.M. Wang, X.R. Liu, H. Tang, L. Bai, Z. Geng, P.R. Song, Z.M. Shi, X.X. Ren, J.C. Su, Engineering large-scale self-mineralizing bone organoids with bone matrix-inspired hydroxyapatite hybrid bioinks, Adv Mater (2024) e2309875.
[87] S.S. Chen, X. Chen, Z. Geng, J.C. Su, The horizon of bone organoid: a perspective on construction and application, Bioact. Mater. 18 (2022) 15–25.
[88] X.Y. Jia, X. Fan, C. Chen, Q.Y. Lu, H.F. Zhou, Y.M. Zhao, X.G. Wang, S.Y. Han, L.L. Ouyang, H.J. Yan, H.L. Dai, H.Y. Geng, Chemical and structural engineering of gelatin-based delivery systems for therapeutic applications: a review, Biomacromolecules 25 (2024) 564–589.
[89] Z. Yang, Z. Yang, L. Ding, P. Zhang, C. Liu, D. Chen, F. Zhao, G. Wang, X. Chen, Self-adhesive hydrogel biomimetic periosteum to promote critical-size bone defect repair via synergistic osteogenesis and angiogenesis, ACS Appl. Mater. Interfaces 14 (2022) 36395–36410.
[90] Y. Honda, Y. Takeda, P. Li, A. Huang, S. Sasayama, E. Hara, N. Uemura, M. Ueda, M. Hashimoto, K. Arita, N. Matsumoto, Y. Hashimoto, S. Baba, T. Tanaka, Epigallocatechin gallate-modified gelatin sponges treated by vacuum heating as a novel scaffold for bone tissue engineering, Molecules 23 (2018) 876.
[91] L.E. Valencia-Gómez, H. Reyes-Blas, J.F. Hernández-Paz, C.A. Rodríguez-González, I. Olivas-Armendáriz, Comparative study of the antibacterial, biodegradable, and biocompatibility properties of composite and bi-layer films of chitosan/gelatin coated with silver particles, Materials 16 (2023) 3000.
[92] R. Yin, C. Zhang, Y.Y. Chen, Y. Wang, Q. Feng, Y.M. Liu, M.H. Yu, Y.H. Yuan, C.Y. Xu, F.H. Liu, W.W. Zhao, Transient, printable and recyclable gelatin hydrogels with enhanced mechanical sensing and electromagnetic shielding performance by incorporation of reduced graphene oxide, Chem Eng J 475 (2023) 145794.
[93] B. Safari, A. Aghanejad, J. Kadkhoda, M. Aghazade, L. Roshangar, S. Davaran, Biofunctional phosphorylated magnetic scaffold for bone tissue engineering, Colloid Surfaces B. 211 (2022) 112284.
[94] S. Kalidas, S. Sumathi, Mechanical, biocompatibility and antibacterial studies of gelatin/polyvinyl alcohol/silkfibre polymeric scaffold for bone tissue engineering, Heliyon 9 (2023) e16886.
[95] H. Chen, R. Feng, T. Xia, Z. Wen, Q. Li, X. Qiu, B. Huang, Y. Li, Progress in surface modification of titanium implants by hydrogel coatings, Gels 9 (2023) 423.
[96] A. Aguilar, N. Zein, E. Harmouch, B. Hafdi, F. Bornert, D. Offner, F. Clauss, F. Fioretti, O. Huck, N. Benkirane-Jessel, G. Hua, Application of chitosan in bone and dental engineering, Molecules 24 (2019) 3009.
[97] A. El-Araby, W. Janati, R. Ullah, S. Ercisli, F. Errachidi, Chitosan, chitosan derivatives, and chitosan-based nanocomposites: eco-friendly materials for advanced applications (a review), Front. Chem. 11 (2024) 1327426.
[98] P. Qi, Z. Ning, X. Zhang, Synergistic effects of 3D chitosan-based hybrid scaffolds and mesenchymal stem cells in orthopaedic tissue engineering, IET Nanobiotechnol. 17 (2023) 41–48.
[99] A. Manzari-Tavakoli, R. Tarasi, R. Sedghi, A. Moghimi, H. Niknejad, Fabrication of nanochitosan incorporated polypyrrole/alginate conducting scaffold for neural tissue engineering, Sci. Rep. 10 (2020) 22012.
[100] S. Ranganathan, K. Balagangadharan, N. Selvamurugan, Chitosan and gelatin-based electrospun fibers for bone tissue engineering, Int. J. Biol. Macromol. 133 (2019) 354–364.
[101] Y. Zhao, Z.S. Zhu, J. Guan, S.J. Wu, Processing, mechanical properties and bio-applications of silk fibroin-based high-strength hydrogels, Acta Biomater. 125 (2021) 57–71.
[102] P. Jiang, J. Ran, P. Yan, L. Zheng, X. Shen, H. Tong, Rational design of a high-strength bone scaffold platform based on in situ hybridization of bacterial cellulose/nano-hydroxyapatite framework and silk fibroin reinforcing phase, J. Biomater. Sci. Polym. Ed. 29 (2018) 107–124.
[103] H. Wu, K. Lin, C. Zhao, X. Wang, Silk fibroin scaffolds: a promising candidate for bone regeneration, Front. Bioeng. Biotechnol. 10 (2022) 1054379.
[104] K.A. Luetchford, J.B. Chaudhuri, P.A. De Bank, Silk fibroin/gelatin microcarriers as scaffolds for bone tissue engineering, Mater Sci Eng C Mater Biol Appl 106 (2020) 110116.
[105] D.C. Bi, X. Yang, J. Lu, X. Xu, Preparation and potential applications of alginate oligosaccharides, Crit Rev Food Sci 63 (2023) 10130–10147.
[106] N. Beheshtizadeh, A. Farzin, S. Rezvantalab, Z. Pazhouhnia, N. Lotfibakhshaiesh, J. Ai, A. Noori, M. Azami, 3D printing of complicated gelma-coated alginate/tri-calcium silicate scaffold for accelerated bone regeneration, Int. J. Biol. Macromol. 229 (2023) 636–653.
[107] L. Cheng, B. Yao, T. Hu, X. Cui, X. Shu, S. Tang, R. Wang, Y. Wang, Y. Liu, W. Song, X. Fu, H. Li, S. Huang, Properties of an alginate-gelatin-based bioink and its potential impact on cell migration, proliferation, and differentiation, Int. J. Biol. Macromol. 135 (2019) 1107–1113.
[108] A. Ressler, Chitosan-based biomaterials for bone tissue engineering applications: a short review, Polymers 14 (2022) 3430.
[109] C.J. Kowalczewski, J.M. Saul, Biomaterials for the delivery of growth factors and other therapeutic agents in tissue engineering approaches to bone regeneration, Front. Pharmacol. 9 (2018) 513.
[110] J. Zhang, S. Suttapreyasri, C. Leethanakul, B. Samruajbenjakun, Fabrication of vascularized tissue-engineered bone models using triaxial bioprinting, J. Biomed. Mater. Res. (2024) 1–14.
[111] Y. Ren, Y. Zhang, H. Zhang, Y. Wang, L. Liu, Q. Zhang, A gelatin-hyaluronic acid double cross-linked hydrogel for regulating the growth and dual dimensional cartilage differentiation of bone marrow mesenchymal stem cells, J. Biomed. Nanotechnol. 17 (2021) 1044–1057.
[112] W. Gao, L. Sun, Z. Zhang, Z. Li, Cellulose nanocrystals reinforced gelatin/bioactive glass nanocomposite scaffolds for potential application in bone regeneration, J. Biomater. Sci. Polym. Ed. 31 (2020) 984–998.
[113] Y. Lu, X. Zhu, C. Hu, P. Li, M. Zhao, J. Lu, G. Xia, A fucoidan-gelatin wound dressing accelerates wound healing by enhancing antibacterial and anti-inflammatory activities, Int. J. Biol. Macromol. 255 (2024) 127899.
[114] L.C.E. da Silva, B.A. Más, E.A.R. Duek, R. Landers, C.A. Bertran, M.C. Gonçalves, Amphiphilic nucleating agents to enhance calcium phosphate growth on polymeric surfaces, Langmuir 33 (2017) 3855–3863.
[115] C. Yuan, X. Ren, H. Ye, S. Jin, Y. Zuo, J. Li, Y. Li, Physicochemical and in vitro degradation behaviors of fibrous membranes with different polycaprolactone and gelatin proportions, J. Nanosci. Nanotechnol. 20 (2020) 7376–7384.
[116] K.P. Zhou, Z.C. Zhang, J.W. Xue, J.M. Shang, D.J. Ding, W.F. Zhang, Z.J. Liu, F. Yan, N. Cheng, Hybrid Ag nanoparticles/polyoxometalate-polydopamine nano-flowers loaded chitosan/gelatin hydrogel scaffolds with synergistic photothermal/chemodynamic/Ag^{+} anti-bacterial action for accelerated wound healing, Int. J. Biol. Macromol. 221 (2022) 135–148.
[117] D. Sakarya, T. Zorlu, S. Yücel, Y.M. Sahin, A.C. Özarslan, Advanced bioresin formulation for 3D-printed bone scaffolds: PCLDMA and p-PLA integration, Polymers 16 (2024) 534.
[118] S.Z. Shi, X. Xu, X.Z. He, S.Y. Fan, P.R.F. Liu, C.W. Wu, K. Cheng, PVTF nanoparticles/PLA electroactive degradable membrane for bone tissue regeneration, Coatings 14 (2024) 115.
[119] F. Yu, M. Li, Z. Yuan, F. Rao, X. Fang, B. Jiang, Y. Wen, P. Zhang, Mechanism research on a bioactive resveratrol pla-gelatin porous nano-scaffold in promoting the repair of cartilage defect, Int J Nanomedicine 13 (2018) 7845–7858.
[120] M. Hassan, H.A. Abdelnabi, S. Mohsin, Harnessing the potential of PLGA nanoparticles for enhanced bone regeneration, Pharmaceutics 16 (2024) 273.
[121] S. Xu, G. Tian, M. Zhi, Z. Liu, Y. Du, X. Lu, M. Li, J. Bai, X. Li, J. Deng, S. Ma, Y. Wang, Functionalized PLGA microsphere loaded with fusion peptide for therapy of bone defects, ACS biomater sci eng 10 (2024) 2463–2476.
[122] K.S. Ogueri, K.S. Ogueri, A. McClinton, H.M. Kan, C.C. Ude, M.A. Barajaa, H.R. Allcock, C.T. Laurencin, In vivo evaluation of the regenerative capability of glycylglycine ethyl ester-substituted polyphosphazene and poly (lactic-co-glycolic acid) blends: a rabbit critical-sized bone defect model, ACS Biomater. Sci. Eng. 7 (2021) 1564–1572.

[123] M.G.L. Olthof, D.H.R. Kempen, J.L. Herrick, M.J. Yaszemski, W.J.A. Dhert, L. Lu, Effect of different sustained bone morphogenetic protein-2 release kinetics on bone formation in poly (propylene fumarate) scaffolds, J. Biomed. Mater. Res. B Appl. Biomater. 106 (2018) 477–487.
[124] X. Li, X. Liu, S. Ni, Y. Liu, H. Sun, Q. Lin, Enhanced osteogenic healing process of rat tooth sockets using a novel simvastatin-loaded injectable microsphere-hydrogel system, J. Cranio-Maxillo-Fac. Surg. 47 (2019) 1147–1154.
[125] E.C. Rodríguez-Merchán, Bone healing materials in the treatment of recalcitrant nonunions and bone defects, Int. J. Mol. Sci. 23 (2022) 3352.
[126] J. Gao, M. Li, J. Cheng, X. Liu, Z. Liu, J. Liu, P. Tang, 3D-printed GelMA/PEGDA/F127DA scaffolds for bone regeneration, J. Funct. Biomater. 14 (2023) 96.
[127] M.N. Gomez-Cerezo, N. Perevoshchikova, R. Ruan, K.M. Moerman, R. Bindra, D.G. Lloyd, M.H. Zheng, D.J. Saxby, C. Vaquette, Additively manufactured polyethylene terephthalate scaffolds for scapholunate interosseous ligament reconstruction, Biomater. Adv. 149 (2023) 213397.
[128] Y. Huang, X. Zhai, T. Ma, M. Zhang, H. Yang, S. Zhang, J. Wang, W. Liu, X. Jin, W.W. Lu, X. Zhao, W. Hou, T. Sun, J. Shen, H. Pan, Y. Du, C.H. Yan, A unified therapeutic-prophylactic tissue-engineering scaffold demonstrated to prevent tumor recurrence and overcoming infection toward bone remodeling, Adv Mater 35 (2023) e2300313.
[129] Q. Hu, R. Lu, S. Liu, Y. Liu, Y. Gu, H. Zhang, 3D printing GelMA/PVA interpenetrating polymer networks scaffolds mediated with CuO nanoparticles for angiogenesis, Macromol. Biosci. 22 (2022) e2200208.
[130] X.Q. Zheng, Y.F. Wang, J.Y. Liu, J.T. Han, Z.D. Cui, S.L. Wu, Y.Q. Liang, S.L. Zhu, X. Ge, Z.Y. Li, Gelatin/gentamicin sulfate-modified PMMA bone cement with proper mechanical properties and high antibacterial ability, Mater. Res. Express 9 (2022) 035405.
[131] Y.T. Wu, X. Zhang, B.W. Tan, Y. Shan, X. Zhao, J.F. Liao, Near-infrared light control of GelMA/PMMA/PDA hydrogel with mild photothermal therapy for skull regeneration, Biomater. Adv. 133 (2022) 112641.
[132] Q.H. Guo, S.S. Yang, G.Q. Ni, J.L. Ji, M.W. Luo, W. Du, M. Wiens, The preparation and effects of organic-inorganic antioxidative biomaterials for bone repair, Biomedicines 12 (2024) 70.
[133] W.B. Zhu, C. Li, M.X. Yao, X.M. Wang, J. Wang, W. Zhang, W. Chen, H.Z. Lv, Advances in osseointegration of biomimetic mineralized collagen and inorganic metal elements of natural bone for bone repair, Regen Biomater 10 (2023) rbad030.
[134] L. Sutrisno, H.J. Chen, Y.Z. Chen, T. Yoshitomi, N. Kawazoe, Y.N. Yang, G.P. Chen, Composite scaffolds of black phosphorus nanosheets and gelatin with controlled pore structures for photothermal cancer therapy and adipose tissue engineering, Biomaterials 275 (2021) 120923.
[135] D. Ozhava, P. Winkler, Y. Mao, Enhancing antimicrobial activity and reducing cytotoxicity of silver nanoparticles through gelatin nanoparticles, Nanomedicine. 19 (2024) 199–211.
[136] M.S. Aghajanzadeh, R. Imani, M.H. Nazarpak, S.J.P. McInnes, Augmented physical, mechanical, and cellular responsiveness of gelatin-aldehyde modified xanthan hydrogel through incorporation of silicon nanoparticles for bone tissue engineering, Int. J. Biol. Macromol. 259 (2024) 129231.
[137] O. Suzuki, R. Hamai, S. Sakai, Corrigendum to "The material design of octacalcium phosphate bone substitute: increased dissolution and osteogenecity, Acta Biomater. 161 (2023) 325.
[138] S. Kumari, D. Singh, P. Srivastava, B.N. Singh, A. Mishra, Generation of graphene oxide and nano-bioglass based scaffold for bone tissue regeneration, Biomed Mater 17 (2022) 065012.
[139] G.E.D. Blanco, C.W.O. de Souza, M.P. Bernardo, M. Zenke, L.H.C. Mattoso, F.K.V. Moreira, Antimicrobially active gelatin/[Mg-Al-CO_3]-LDH composite films based on clove essential oil for skin wound healing, Mater. Today Commun. 27 (2021) 102169.
[140] W.F. Lee, S.C. Lee, Effect of hydrotalcite on the swelling and mechanical behaviors for the hybrid nanocomposite hydrogels based on gelatin and hydrotalcite, J. Appl. Polym. Sci. 100 (2006) 500–507.
[141] M. Arumugam, B. Murugesan, P. Balasekar, S.P. Malliappan, D.K. Chinnalagu, K. Chinniah, Y.R. Cai, S. Mahalingam, Silk fibroin and gelatin composite nanofiber combined with silver and gold nanoparticles for wound healing accelerated by reducing the inflammatory response, Process Biochem 134 (2023) 1–16.
[142] S. Chen, X.X. Du, T.L. Wang, L. Jia, D. Huang, W.Y. Chen, Synthesis of near-infrared responsive gold nanorod-doped gelatin/hydroxyapatite composite microspheres with controlled photo-thermal property, Ceram. Int. 44 (2018) 900–904.
[143] C.J. Gao, S.J. Huo, X.L. Li, X.D. You, Y. Zhang, J.P. Gao, Characteristics of calcium sulfate/gelatin composite biomaterials for bone repair, J Biomat Sci-Polym E. 18 (2007) 799–824.
[144] Y. Chen, T. Zhang, Q. Zhang, Q.J. Lei, S.J. Gao, K.W. Xiao, F.F. Yan, L. Cai, A composite of cubic calcium-magnesium sulfate and bioglass for bone repair, Front Bio Biotech 10 (2022) 898951.
[145] B. Wang, S. Peng, H. Chen, H. Ren, Y. Yan, Q. Zhang, Regulating the release of Mg-MOF from degradable bone cement by coating Mg-MOF with oxidized dextran/gelatin, New J. Chem. 47 (2023) 18591–18602.
[146] W.Y. Dong, W.D. Ma, S.S. Zhao, X.Y. Zhou, Y.L. Wang, Z.W. Liu, D.H. Sun, M. Zhang, Z.H. Jiang, Multifunctional 3D sponge-like macroporous cryogel-modified long carbon fiber reinforced polyetheretherketone implants with enhanced vascularization and osseointegration, J. Mater. Chem. B 10 (2022) 5473–5486.
[147] L.Y. Li, S. Qin, J. Peng, A. Chen, Y. Nie, T.Q. Liu, K.D. Song, Engineering gelatin-based alginate/carbon nanotubes blend bioink for direct 3D printing of vessel constructs, Int. J. Biol. Macromol. 145 (2020) 262–271.
[148] J. Shi, W. Dai, A. Gupta, B. Zhang, Z. Wu, Y. Zhang, L. Pan, L. Wang, Frontiers of hydroxyapatite composites in bionic bone tissue engineering, Materials 15 (2022) 8475.
[149] X. Pu, L. Tong, X. Wang, Q. Liu, M. Chen, X. Li, G. Lu, W. Lan, Q. Li, J. Liang, Y. Sun, Y. Fan, X. Zhang, Bioinspired hydrogel anchoring 3DP GelMA/HAp scaffolds accelerates bone reconstruction, ACS Appl. Mater. Interfaces 14 (2022) 20591–20602.
[150] B. Conrad, F. Yang, Hydroxyapatite-coated gelatin microribbon scaffolds induce rapid endogenous cranial bone regeneration in vivo, Biomater. Adv. 140 (2022) 213050.
[151] A.C. Özarslan, S. Yücel, Comprehensive assessment of SrO and CuO co-incorporated 50S6P amorphous silicate bioactive glasses in vitro: revealing bioactivity properties of bone graft biomaterial for bone tissue engineering applications, Ceram. Int. 49 (2023) 13940–13952.
[152] H. Mostajeran, N. Baheiraei, H. Bagheri, Effects of cerium-doped bioactive glass incorporation on an alginate/gelatin scaffold for bone tissue engineering: in vitro characterizations, Int. J. Biol. Macromol. 255 (2024) 128094.
[153] Q.M. Ou, K.Q. Huang, C.Q. Fu, C.L. Huang, Y.F. Fang, Z.P. Gu, J. Wu, Y. Wang, Nanosilver-incorporated halloysite nanotubes/gelatin methacrylate hybrid hydrogel with osteoimmunomodulatory and antibacterial activity for bone regeneration, Chem Eng J 382 (2020) 123019.
[154] H. Katas, M.A.M. Akhmar, S.S.I. Abdalla, Biosynthesized silver nanoparticles loaded in gelatine hydrogel for a natural antibacterial and anti-biofilm wound dressing, J Bioact Compat Pol. 36 (2021) 111–123.
[155] W.Y. Qi, R. Zhang, Z.S. Wang, H.T. Du, Y.W. Zhao, B. Shi, Y. Wang, X. Wang, P. Wang, Advances in the application of black phosphorus-based composite biomedical materials in the field of tissue engineering, Pharmaceuticals 17 (2024) 242.
[156] X. Jing, C. Xu, W. Su, Q. Ding, B. Ye, Y. Su, K. Yu, L. Zeng, X. Yang, Y. Qu, K. Chen, T. Sun, Z. Luo, X. Guo, Photosensitive and conductive hydrogel induced innerved bone regeneration for infected bone defect repair, Adv Healthc Mater 12 (2023) e2201349.
[157] K. Li, B.L. Tao, H.C. Tian, J.J. Wu, K. Huang, C.P. Yan, S.A. Chen, A. Guo, D.M. Jiang, Titanium implants with antiaging effect to repair senile osteoporosis fracture, Mater Design 232 (2023) 112071.
[158] K.H. Luk, C.H. Chan, Z.W. Liu, C.W. Jiao, X.B. Yang, X.L. Dong, K.H. Wong, Selenium nanoparticles functionalized by mushroom polysaccharide-protein complex: a novel nano-mineral for managing postmenopausal osteoporosis, J. Funct.Foods 110 (2023) 105832.
[159] L. Bai, M.G. Feng, Q.W. Zhang, Z.W. Cai, Q.M. Li, Y. Li, C. Ma, J.A. Xiao, Y.F. Lin, Synergistic osteogenic and antiapoptotic framework nucleic acid complexes prevent diabetic osteoporosis, Adv. Funct. Mater. 34 (2024).

[160] B. Zhou, X. Jiang, X. Zhou, W. Tan, H. Luo, S. Lei, Y. Yang, GelMA-based bioactive hydrogel scaffolds with multiple bone defect repair functions: therapeutic strategies and recent advances, Biomater. Res. 27 (2023) 86.
[161] X.Y. Huang, Y.X. Lou, Y.H. Duan, H. Liu, J. Tian, Y. Shen, X. Wei, Biomaterial scaffolds in maxillofacial bone tissue engineering: a review of recent advances, Bioact. Mater. 33 (2024) 129–156.
[162] J. Quek, C. Vizetto-Duarte, S.H. Teoh, Y. Choo, Towards stem cell therapy for critical-sized segmental bone defects: current trends and challenges on the path to clinical translation, J. Funct. Biomater. 15 (2024) 145.