BioMedical Engineering OnLine

REVIEW Open Access

Antioxidant scaffolds for enhanced bone regeneration: recent advances and challenges

Hui Li[1†], Zhenhe Zhang[1,2†], Jing Liu[1*] and Huiwen Wang[1*]

[†]Hui Li and Zhenhe Zhang have contributed equally to this work.

*Correspondence: 233232312@qq.com; 416919029@qq.com

[1] Department of Orthopedics, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1277 Jiefang Avenue, Wuhan 430022, China
[2] Hubei Province Key Laboratory of Oral and Maxillofacial Development and Regeneration, Wuhan 430022, China

Abstract

Bone regeneration is integral to maintaining bone function and integrity in the body, as well as treating bone diseases, such as osteoporosis and defects. However, oxidative stress often poses a significant obstacle during bone regeneration, leading to cell damage, inflammatory responses, and subsequent impediment of normal bone tissue formation. Therefore, to maintain bone regeneration, antioxidant therapy is essential. Bone scaffolds, serving as a temporary support for bone tissue, can provide an ideal microenvironment for cell proliferation and differentiation, effectively promoting bone tissue formation. In recent years, with in-depth research on antioxidants and their mechanisms of action, the development and application of antioxidant bone scaffolds have shown tremendous potential. These antioxidant bone scaffolds not only promote osteogenic differentiation and angiogenesis, but also effectively inhibit the inflammatory response and osteoclast formation, significantly improving the efficiency of bone regeneration. Notably, with the rapid development of nanotechnology, nanozymes with multi-enzyme-like activities have been successfully constructed and encapsulated within bone scaffolds, leading to the proposal of multifunctional antioxidant strategies. Therefore, this review summarizes recent research progress, categorically introducing types of bone scaffolds and antioxidants, elucidating therapeutic strategies of antioxidant bone scaffolds, and identifying current challenges, aiming to provide valuable guidance for subsequent research.

Keywords: Bone tissue engineering, Oxidative stress, Antioxidant strategy, Smart bone scaffold, Nanozyme

Introduction

Bone tissue possesses a natural regenerative capacity, initiating an orderly repair process to restore bone integrity once its integrity is compromised [1]. However, this spontaneous repair ability is limited and cannot cope with critical-sized bone defects [2]. Clinically, the treatment of bone defects includes methods, such as autologous bone grafting and allogeneic bone grafting, yet each of these methods has its limitations [3]. Autologous bone grafting is constrained by secondary damage to the donor site and limited availability, whereas allogeneic bone grafting faces the risk of immune rejection [4]. Therefore, the search for a bone regeneration treatment that overcomes

the shortcomings of existing therapies has become a central theme in bone regeneration research.

Bone scaffolds play an increasingly important role in bone repair as a novel therapeutic approach [5]. Currently, bone scaffolds including metal scaffolds, ceramic scaffolds, polymer scaffolds, and composite scaffolds are widely constructed and studied, which can mimic the structural and mechanical properties of natural bone [6]. Bone scaffolds can guide cell adhesion, migration, and proliferation, promote bone tissue repair, and shorten the treatment period [7]. Compared to traditional bone defect treatments, bone scaffolds have the advantage of being personalizable as the scaffold can be tailored to the size and shape of the bone defect site [8]. Some bone scaffolds also have the advantages of adjustable composition, structure and mechanical properties, and act as carriers for drugs and growth factors to achieve slow release of drugs and local treatment, thus greatly improving their biological activity and providing a good basis for their application in bone regeneration [9].

Bone repair involves the coordinated participation of multiple cells, such as bone-marrow-derived mesenchymal stem cells (BMSCs), immune cells, and endothelial cells [10]. Redox homeostasis is critical in this process. Typically, there is an intracellular oxidative defense system that includes endogenous antioxidant enzymes and low molecular weight scavengers (e.g., vitamins, coenzyme Q, selenium, and zinc) [11]. They achieve reactive oxygen species (ROS) scavenging by inhibiting ROS production or catalyzing the ROS reaction to maintain cellular redox homeostasis as a means to ensure cellular function and orderly bone repair. However, under unfavorable conditions, such as diabetes, infections, and metabolic diseases, the intracellular oxidative defense system tends to fail, leading to accumulation of intracellular ROS, loss of function, and even cell death, which greatly impedes bone regeneration [12, 13]. Therefore, there is an urgent need to develop antioxidant-based bone regeneration therapies.

Given the importance of redox homeostasis for bone regeneration and the advantages of bone scaffolds in bone regeneration, a number of antioxidant bone scaffolds have been constructed in recent years [14, 15]. Many typical antioxidant scaffolds are based on previous pharmacological studies, where natural substances or enzymes with antioxidant properties are encapsulated within bone scaffolds to endow them with antioxidant capabilities [15, 16]. With the advancement of nanoscience, a series of nanozymes with tunable size and composition have been developed and loaded into bone scaffolds [17, 18]. The encapsulation of nanozymes endows these scaffolds with efficient ROS scavenging efficiency and diversified functions, providing new ideas and methods for antioxidant therapy in bone regeneration.

Currently, research on antioxidant bone scaffolds has been increasing, but there is still a lack of summarization. Here, we review the progress of research on antioxidant scaffolds in bone regeneration. First, we introduce the negative impacts of oxidative stress during the bone repair process. Subsequently, we summarize the types of antioxidants and scaffolds. Based on this foundation, we explore the therapeutic strategies of antioxidant bone scaffolds based on different functions and review the progress of cutting-edge smart antioxidant scaffolds. Finally, we identify the limitations of current research and propose prospects for future research directions, aiming to provide valuable references and insights for subsequent scientific explorations.

Bone repair and oxidative stress

Typically, once bone tissue is damaged, blood collects at the site of the bone injury to form a hematoma [19]. Subsequently, immune cells, including macrophages, neutrophils, and lymphocytes, rapidly recruit to the site, triggering an inflammatory response to clear bone debris and resist infection [4]. In the early stages of inflammation, bone repair-related cells such as BMSCs, vascular endothelial cells, and fibroblasts are recruited to the site of bone injury under the mediation of cytokines secreted by immune cells [20]. Several days after bone injury, inflammation gradually subsides, and macrophages transition from the M1 to the M2 phenotype, secreting anti-inflammatory factors and growth factors that promote the proliferation and differentiation of bone repair-related cells [21]. During the bone formation phase, granulation tissue is gradually replaced by fibrous tissue, forming fibrous callus. Subsequently, depending on the location of the bone injury, endochondral ossification or intramembranous ossification occurs to form the initial bone [22]. Finally, under mechanical stimulation, osteoblasts and osteoclasts act synergistically to achieve bone remodeling through orderly bone resorption and formation, restoring the normal structure of the bone [23].

Diabetes, hormonal fluctuations (such as the decline in estrogen levels after menopause), infections, inflammation, and the natural aging process are all factors that may trigger oxidative stress, posing significant challenges to the repair of bone defects [24, 25]. The excessive generated ROS damages the DNA, proteins, and lipids of BMSCs and osteoblasts, disrupting their differentiation function, and reducing the synthesis and mineralization of the bone matrix, thereby hindering the formation of new bone [26]. Furthermore, oxidative stress can also inhibit the proliferation, migration, and tube formation ability of vascular endothelial cells, impeding angiogenesis, a critical step in the bone regeneration process [27, 28]. Under the influence of oxidative stress, immune cells at the bone defect site continue to be activated and secrete pro-inflammatory factors, thus creating a vicious circle that further exacerbates oxidative stress and makes it difficult for the bone defect site to transition from an inflammatory state to a regenerative state [29]. In addition, the excessive accumulation of ROS can also activate the RANKL/OPG pathway, promoting the formation and activation of osteoclasts, exacerbating bone loss, and further worsening the condition of bone defects [30]. It is worth noting that even bone implants used as therapeutic treatments may trigger local inflammation in the periphery after implantation, which in turn induces cellular oxidative stress and adversely affects the bone repair process [31, 32]. Therefore, the application of antioxidant therapy in the field of bone regeneration holds broad potential value in the treatment of bone defect repair.

Classification of bone scaffolds

Bone scaffolds including metal scaffolds, ceramic scaffolds, polymer scaffolds, and composite scaffolds are currently commonly used scaffolds for bone tissue engineering [6]. Metal bone scaffolds, such as titanium (Ti), magnesium, zinc, and stainless steel, are widely used for bone defect repair due to their excellent mechanical properties and biocompatibility [33]. Traditionally, titanium and its alloys are most commonly used due to their biologically inert nature. However, their lack of biodegradability often requires

secondary surgery for removal [34]. In recent years, magnesium alloys and zinc alloys have gained attention due to their biodegradability and bioactivity [35]. Among them, magnesium-based scaffolds exhibit mechanical strength similar to bone and release magnesium ions, which promote bone integration and vascularized bone regeneration [36]. Similarly, zinc ions released from zinc-based scaffolds play an important regulatory role in the composition of zinc finger proteins and various enzymes [37, 38]. It is worth noting that surface modification and alloying techniques can help regulate the degradation rate and mechanical strength of metal bone scaffolds, thereby improving their biocompatibility and osteointegration capacity, showing potential in bone regeneration [39].

Ceramic scaffolds, including calcium phosphate, hydroxyapatite, and bioactive glass, mimic the composition of natural bone minerals and possess good osteoconductivity and osteoinductivity [40]. Among them, calcium phosphate and hydroxyapatite scaffolds release calcium ions and phosphate ions, which are major components of bone tissue. These ions can regulate the proliferation and differentiation of osteoblast lineage and facilitate rapid bone formation on the scaffold surface [41]. Similarly, bioactive glass, as a type of silicate glass, can react with the physiological environment, releasing ions such as calcium, phosphate, and silicon that promote bone formation [42]. These ceramic scaffolds can further enhance their bioactivity and osteointegration capacity through ion doping, surface modification, and optimization of microstructure, making them highly promising for bone regeneration [43, 44].

Polymer scaffolds, as three-dimensional network structures similar to the extracellular matrix, have gained considerable attention in bone tissue engineering in recent years due to their ability to support cell adhesion and growth [45]. Commonly used polymer scaffolds for bone regeneration include polysaccharides (e.g., hyaluronic acid, alginate, chitosan, and cellulose), proteins (e.g., gelatin, fibronectin, and collagen), and synthetic polymers (e.g., polylactic acid, polycaprolactone, polyurethane, and polyethylene glycol) [46]. Owing to their mild fabrication methods, appropriate degradation characteristics, and drug release kinetics, these polymer scaffolds are well-suited for delivering bioactive molecules, such as natural enzymes and growth factors [47, 48]. Furthermore, stable functionalized scaffolds can be obtained by modifying the polymer molecules, which helps to improve the bioactivity and mechanical properties of the scaffolds [49]. Particularly in recent years, hydrogel scaffolds based on dynamic chemical bonds have been extensively developed, enabling these scaffolds to respond to the pH, glucose, and ROS in the bone microenvironment, achieving intelligent and controllable drug release properties, which further facilitate bone tissue repair [50].

Although metals, ceramics, and polymers exhibit good bone regeneration properties as scaffolds, they still have some limitations. For example, metal scaffolds lack bioactivity, and polymer scaffolds have inadequate mechanical properties [51, 52]. Therefore, in recent years, a series of studies have been devoted to constructing composite material scaffolds. For instance, bioactive glass coatings have been applied to metal scaffolds to enhance their bioactivity, and nano-ceramic particles have been added to polymer scaffolds to improve their mechanical properties [53–55]. In summary, the design of composite bone scaffolds aims to combine the advantages of multiple materials, thereby improving the efficiency of bone repair.

Antioxidants

Nonenzymatic antioxidants

Currently, widely used nonenzymatic antioxidants encompass a variety of natural compounds, such as vitamins (e.g., vitamin C and vitamin E), polyphenols (e.g., quercetin and anthocyanins), carotenoids, and melatonin [56]. These antioxidants not only have a wide range of sources and low production costs but also demonstrate excellent stability and high biocompatibility, making them ideal adjuncts for bone regeneration. When these antioxidants are applied, they effectively activate signaling pathways associated with oxidative stress, such as Nrf2/Keap1, thereby upregulating the expression of various antioxidant enzymes, including superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and heme oxygenase-1 (HO-1) [57]. The increased expression of these enzymes significantly increased the cellular scavenging of ROS and effectively attenuated oxidative stress damage to bone tissue. Some antioxidants, such as polyphenols, can also clear ROS through reactions with free radicals and chelation of metal catalysts [11]. It is noteworthy that during the process of bone regeneration, some nonenzymatic antioxidants demonstrate the potential to promote the proliferation and differentiation of bone progenitor cells [58, 59]. Through their antioxidant properties and regulation of cellular metabolism and function, these antioxidants contribute to accelerating the regeneration of bone tissue, playing a positive role in bone defect repair [59]. Moreover, certain antioxidants exhibit multifunctional characteristics during bone regeneration. Besides their role in combating oxidative stress, they also exert multiple effects, such as antibacterial, anti-inflammatory, and promotion of angiogenesis [60, 61]. This multidimensional regulatory mechanism makes these antioxidants have broader prospects for application in the field of bone regeneration.

Enzymatic antioxidants

Enzymatic antioxidants constitute a category of enzymes with specific catalytic activity that can directly participate in redox reactions, converting ROS into non-toxic substances, thereby protecting cells from oxidative stress damage. Common natural antioxidant enzymes include SOD, CAT, and GPx [62]. Among them, SOD catalyzes the dismutation of superoxide anion into H_2O_2 and O_2, while both CAT and GPx possess the ability to eliminate H_2O_2. Although these natural enzymes exist in human cells, under certain conditions unfavorable for bone regeneration, such as infection or diabetes, the expression of intracellular antioxidant enzymes may decrease [63]. Once the antioxidant system fails to clear ROS, ROS accumulation leads to oxidative stress, further reducing the expression of endogenous antioxidant enzymes in cells, resulting in a vicious cycle. Therefore, delivering natural enzymes directly to the site of bone injury can compensate for the inadequate expression of endogenous antioxidant enzymes in cells and enhance local antioxidant capacity.

Nanozymes

The complex synthesis and purification, high production and storage costs, and poor stability of natural enzymes limit their further application [64]. Therefore, in recent years, nanozymes have gradually been considered as a potential alternative to

natural antioxidant enzymes. Compared to natural enzymes, nanozymes can be easily constructed through simple chemical reactions and possess high catalytic activity as well as excellent stability, and are able to withstand fluctuations in the pH of the tissue microenvironment [65]. Currently, nanozymes used to mimic antioxidant enzymes mainly consist of variable-value metal-based materials, such as cerium, manganese, and molybdenum [66, 67]. They can mimic the activities of enzymes such as SOD, CAT, and GPx to eliminate ROS. It is worth noting that some nanozymes can exhibit multiple enzyme-like activities simultaneously, enabling the construction of cascade reaction systems [3]. In conclusion, nanozymes have provided numerous innovative opportunities for antioxidant therapy in tissue regeneration, thereby driving the conception and implementation of novel bone regeneration strategies.

Antioxidant bone scaffolds

Clinically, existing bone scaffolds (such as titanium and titanium alloys) are typically biologically inert, with their primary functions being to provide mechanical support and limited osteoconduction [68]. When these scaffolds are used, bone repair still depends on the body's intrinsic bone healing capacity. However, in specific conditions, such as infections, diabetes, or aging, elevated oxidative stress disrupts the balance of the bone microenvironment, leading to delayed bone healing or even bone nonunion [69, 70]. In contrast, antioxidant bone scaffolds reverse oxidative stress-induced imbalances in osteoblast and osteoclast activity, persistent inflammatory activation, and impaired angiogenesis by scavenging ROS, therefore, enhancing the body's bone repair capacity [71–73]. Due to the restoration of cellular functions, antioxidant scaffolds exhibit advantages in bone integration and healing time, thereby providing a more ideal solution for bone regeneration.

Currently, antioxidant bone scaffolds are primarily based on metal, ceramic, and polymer materials, which typically lack inherent antioxidant properties. After selecting appropriate base materials, it is necessary to introduce antioxidants into bone scaffolds through methods, such as direct mixing, surface modification, chemical bonding, or nanoparticle loading to endow them with antioxidant characteristics [74]. The prepared scaffolds should undergo clear evaluations of mechanical properties, pore size, percentage porosity, degradation performance, and antioxidant release properties [75]. Furthermore, in vitro and in vivo experiments are required to verify the biosafety, antioxidant properties, and bone regeneration-promoting effects of the scaffolds. At present, a series of antioxidant bone scaffolds have been constructed and have demonstrated excellent ability to alleviate oxidative stress and effectively promote bone regeneration in experiments [76, 77]. Therefore, the composition and function of some typical antioxidant bone scaffolds are described (Table 1). Subsequently, we introduced antioxidant bone scaffolds according to treatment strategies (Fig. 1).

Antioxidant strategies targeting osteoblast lineage

The osteoblast lineage plays a central role in bone regeneration. During the process of bone regeneration, BMSCs are recruited to the site of injury, where they differentiate into osteoblasts under the regulation of growth factors [86]. Osteoblasts are capable of synthesizing bone matrix and forming osteocalcin nodules, and eventually transform

Table 1 Representative antioxidant scaffolds for bone regeneration

Bone scaffold	Antioxidants	Outcome	Refs.
Salicin-laden PCL	Salicin	The scaffold exhibited potent free radical scavenging activity, promoted osteogenic differentiation of BMSCs, and accelerated rats' femoral defect repair	[78]
Titanium rods with procyanidin/mucin coating	Procyanidin	The surface coating of the implant effectively alleviated the oxidative stress induced by H_2O_2 in BMSCs and promoted the osteogenic differentiation of BMSCs by activating Wnt/β-Catenin signaling pathway, which ultimately accelerated in vivo osteogenesis	[79]
OD-MHA/Mg	OD	OD-MHA slowed down the degradation of Mg scaffolds and avoided oxidative stress and MC3T3-E1 cells apoptosis induced by large amounts of magnesium ions. In addition, OD-MHA/Mg effectively exerted antibacterial, pro-angiogenic and reduced osteogenic differentiation effects, accelerating the repair of femoral defects	[80]
Astaxanthin–collagen aerogels	Astaxanthin	Aerogels alleviated oxidative stress in BMSCs by activating the NRF2/HO-1 signaling pathway and promoted bone regeneration in rats	[81]
Silibinin-modified hydroxyapatite-coated titanium rods	Silibinin	Silibinin-modified hydroxyapatite-coating activated the SIRT1/SOD2 signaling pathway to alleviate high glucose-induced oxidative stress in MC3T3-E1 cells, promoted the osteogenic differentiation function of MC3T3-E1 cells under high glucose treatment, and accelerated the osseointegration of titanium rods in diabetic rats	[82]
Metal–polyphenolic network-coated scaffolds(PCL, PLA or PEEK)	Catechol	Metal–polyphenolic networks effectively alleviated H_2O_2-induced oxidative stress in MC3T3-E1 cells, promoted calcium nodule formation, and accelerated the repair of cranial defects in rats	[83]
Gelatin–alginate-nCeO_2 hydrogel	CeO_2	Hydrogel scaffolds with SOD and CAT-like activities promoted MC3T3-E1 cell adhesion, proliferation and osteogenic differentiation, and facilitated femoral defect repair in rats	[18]
TPG@ChSMA	TPG	The TPG released from the hydrogel scaffold activated the SIRT1/PI3K/AKT pathway to mediate the clearance of ROS, alleviating the senescence of BMSCs, and promoted the repair of bone defects in aged osteoporotic rats	[84]
MON(CuMn)-Q-J hydrogel	MON(CuMn)-Q	MON(CuMn)-Q possessed sonodynamic antibacterial effects and mediated antioxidant actions through SOD and CAT-like activities as well as quercetin–metal chelation, effectively exerting anti-inflammatory, pro-angiogenic, and bone repair functions	[85]

PCL: polycaprolactone; OD: oxidized dextran; MHA: 3-aminopropyltriethoxysilane and nano-hydroxyapatite doped micro-arc oxidation; PLA: polylactide; PEEK: polyetheretherketone; TPG: tea polyphenol-reduced graphene; ChSMA: methacryloylated chondroitin sulfate

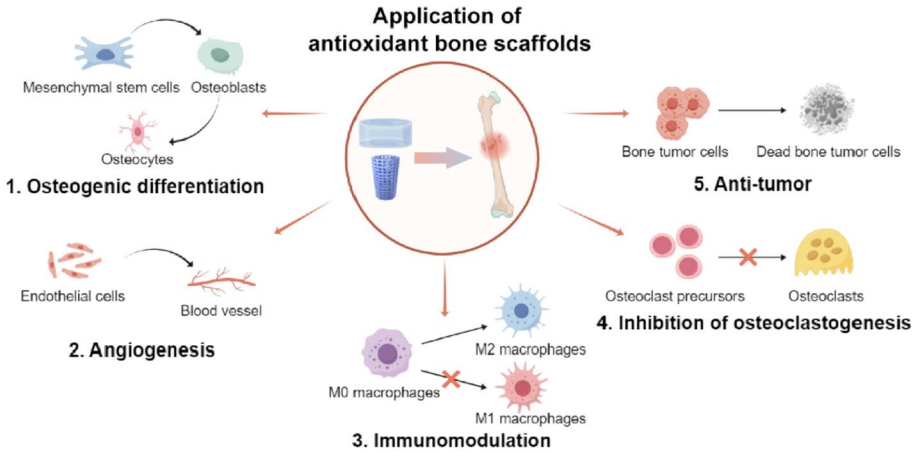

Fig. 1 Therapeutic strategy of antioxidant scaffolds for bone regeneration

into osteocytes that are embedded in the bone matrix to form complete bone tissue [87, 88]. Throughout this process, elevated levels of ROS impair the differentiation and function of osteoblast lineage cells, resulting in reduced mineralization and compromised bone matrix formation [76]. In addition, oxidative stress triggers apoptotic pathways within the osteoblast lineage, reducing osteoblast numbers and hindering bone regeneration, thereby delaying bone repair and exacerbating osteoporosis [89]. In view of this, the introduction of antioxidant bone scaffolds as an innovative strategy to modulate the redox balance holds promise in buffering the negative effects of oxidative stress, maintaining the proliferative capacity and differentiation of the osteoblast lineage, thereby providing a conducive microenvironment for bone regeneration.

Embedding a series of antioxidants capable of directly reacting with ROS into bone scaffolds is a straightforward approach for the construction of antioxidant bone scaffolds [90, 91]. The released antioxidants can be used to scavenge cellular ROS, thus achieving antioxidant effects. Tan et al. have constructed magnesium-seamed C-alkylpyrogallol arene cages (PgC_3Mg) metal–organic cages with ROS scavenging capabilities and incorporated them into gelatin methacrylate (GelMA) hydrogels, resulting in a GelMA/PgC_3Mg composite hydrogel [92]. In this study, the C-alkylpyrogallol arene cages (PgC_3) exhibited efficient ROS scavenging efficiency, effectively reducing the accumulation of ROS in BMSCs induced by H_2O_2. Furthermore, the release of Mg^{2+} from the GelMA/PgC_3Mg hydrogel further promoted the adhesion of BMSCs and the expression of osteogenic-related genes, such as *ALP*, *RUNX2*, *OCN*, and *OPN*, ultimately accelerating the repair of skull defects in rats. Similarly, variable valence metal compounds have attracted widespread attention in the field of bone regeneration as efficient and stable antioxidants. It has been reported that the reversible conversion between Ce(III) and Ce(IV) in CeO_2 nanoparticles (NPs) endows them with SOD and CAT-like activities [93]. Recently, Zhang et al. utilized 3D printing technology to construct a bioactive glass scaffold doped with CeO_2 NPs (CeO_2–BG) (Fig. 2A) [94]. The incorporation of CeO_2 NPs not only imparted antioxidant properties to the scaffold but also enhanced its mechanical performance and promoted the adhesion of osteoblasts and bone-forming capabilities (Fig. 2B–D). Similarly, Liao et al. constructed a GelMA hydrogel

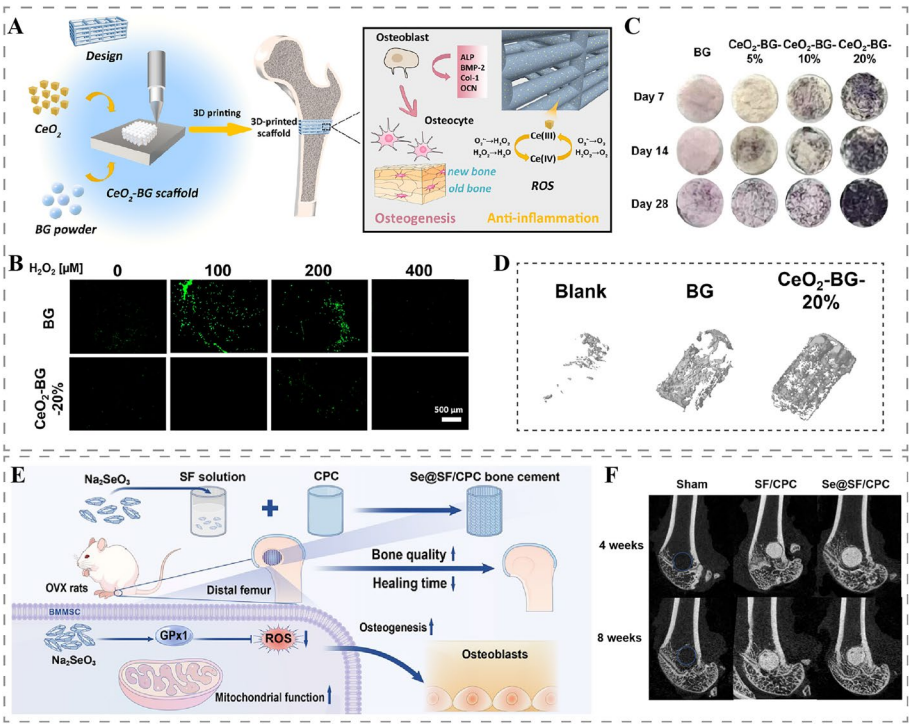

Fig. 2 Antioxidant bone scaffolds for osteogenesis. **A** Schematic illustration of CeO_2–BG scaffolds for antioxidant therapy in bone regeneration. **B** Detection of ROS in osteoblasts by DCFH–DA probe after 1 h of H_2O_2 treatment. Scale bars: 500 μm. **C** ALP staining images of osteoblasts after different times of scaffold treatment. **D** Micro-CT images of rat tibial defects after 12 weeks of scaffold implantation. Adapted from [94], American Chemical Society, 2023. **E** Schematic illustration of the Se@SF/CPC bone scaffold for osteoporotic bone defect repair in ovariectomized rats. **F** Micro-CT images of femoral defects in ovariectomized rats treated with different bone scaffolds. Adapted from [96], Oxford University Press, 2023

containing molybdenum-based polyoxometalate nanoclusters (POM), which possessed ROS scavenging abilities. The GelMA/POM hydrogel also activated the osteogenic differentiation of MC3T3-E1 cells through the PI3K/AKT signaling pathway, promoting bone defect repair in diabetic mice [95].

Although the direct incorporation of antioxidants is one of the most classic methods for constructing antioxidant scaffolds, it has the disadvantage of uncontrolled rapid release of antioxidants from the scaffold [97]. Once the antioxidants are released rapidly, there is a risk of cytotoxicity due to their excessive accumulation, as well as the possibility of being inactivated by the body, leading to a loss of sustained antioxidant effect. To achieve a controlled release of antioxidants and maintain a continuous ROS-scavenging capability, Wang et al. developed a glutathione (GSH)-grafted GelMA hydrogel (GelMA–g-GSH) [98]. Compared to GelMA directly loaded with GSH, GelMA–g-GSH exhibited a slower GSH release rate. GelMA–g-GSH continuously scavenged accumulated ROS in stressed MC3T3-E1 cells through the GSH–GSSG cycle, activated the PI3K/AKT pathway, and promoted osteoblast differentiation and the repair of cranial defects in diabetic mice.

In osteoporotic patients, mitochondrial dysregulation and impaired energy metabolism were present in BMSCs isolated from ovariectomized rats

(OVX–BMSCs), manifested by decreased mitochondrial membrane potential, reduced ATP production, and excessive accumulation of ROS, which led to impaired osteogenic differentiation of BMSCs and disturbed bone regeneration [99]. Therefore, activation of the endogenous antioxidant system of cells through bone scaffolds is considered an effective treatment for osteoporotic bone defects. Recently, Zhou et al. found that Na_2SeO_3 significantly activated the expression of the antioxidant enzyme GPx1 (a selenium-dependent enzyme) in OVX–BMSCs, promoting the restoration of mitochondrial function and reducing intracellular ROS levels [96]. In contrast, silencing GPx1 eliminated the beneficial effects of Na_2SeO_3 on mitochondrial function. Based on this, they developed a Na_2SeO_3-doped silk fibroin/calcium phosphate cement (SF/CPC) scaffold (Se@SF/CPC) (Fig. 2E). The Se@SF/CPC scaffold promoted the expression of alkaline phosphatase and calcium deposition in OVX–BMSCs, thereby accelerating the repair of osteoporotic bone defects (Fig. 2F). It has been reported that melatonin can upregulate intracellular antioxidant genes, such as SOD, CAT, GPx, and HO-1, thereby restoring cellular function through the activation of the endogenous antioxidant system. In another study, Gu et al. developed a silk fibroin scaffold loaded with melatonin (SF@MT) for the treatment of osteoporotic bone defects [100]. The released melatonin can activate the SIRT1/SOD2 pathway in BMSCs from ovariectomized rats, restoring mitochondrial energy metabolism and antioxidant function. This process promoted the differentiation of osteoblasts, matrix synthesis, and mineralization, thereby accelerating the regeneration of bone defects in the femur of ovariectomized rats.

Antioxidant strategies for angiogenesis in bone regeneration

Newly formed blood vessels play a crucial role in bone repair. A series of processes involved in bone regeneration rely on neovascularization, including the recruitment of neutrophils and monocyte/macrophage lineage cells and the homing of stem cells [101, 102]. The newly formed blood vessels can also supply oxygen, nutrients, and growth factors while removing metabolic waste, thereby preventing exacerbated oxidative stress in cells [102]. Chen et al. recently incorporated melatonin-loaded polylactic–co-glycolic acid nanoparticles (MT@PLGA) and sodium alginate hydrogel into polycaprolactone/β-Tricalcium phosphate (PCL/β-TCP) scaffolds to obtain PCL/β-TCP/SA/MT scaffolds [73]. Even under conditions of high glucose-induced stress, PCL/β-TCP/SA/MT scaffolds can still promote endothelial cell proliferation, migration, and tubule formation. This pro-angiogenic effect is associated with the activation of the NRF2/HO-1 signaling pathway, involving downstream antioxidant enzyme activation to alleviate oxidative stress and directly promote vascular endothelial growth factor (VEGF) production. In addition, the scaffold can alleviate oxidative stress in BMSCs, restore their osteogenic differentiation ability, and effectively promote cranial defect repair in diabetic mice.

Type H vessels, a subtype of blood vessels discovered in recent years, are distributed in the epiphysis of bones [103]. They are characterized by endothelial cells with high expression of CD31 and endomucin (Emcn) [104]. Type H vessels are considered major participants in the "vascularization-osteogenesis coupling" process, because they are surrounded by a large number of osteoprogenitors expressing high levels of Osterix and RUNX2. In addition, endothelial cells within type H vessels can secrete cytokines, such as

noggin and VEGF, stimulating the proliferation and differentiation of osteoprogenitors, and thereby promoting bone formation [104, 105]. Recently, Zhou et al. synthesized a hydrogel composed of GelMA, acrylyl-β-cyclodextrin, and reduced graphene oxide functionalized with β-cyclodextrin (GM/Ac-CD/rGO0.6) [106]. Application of GM/Ac-CD/rGO0.6 in vivo was found to effectively eliminate ROS accumulation at the edge of cranial defects, thereby promoting bone regeneration in vivo. Importantly, there was also increased formation of type H vessels in the treatment group. Further RNA-seq evaluation revealed that GM/Ac-CD/rGO0.6 cleared excessive ROS accumulation in stressed human umbilical vein endothelial cells (HUVECs) and activated the miR-200C/ZEB1/Notch1 signaling pathway to increase the formation of type H vessels, thereby contributing to bone tissue regeneration.

Antioxidant therapy combined with bone immunomodulation strategies

Bone regeneration is closely related to immunity. Among the various immune cells involved in bone repair processes, macrophages play a pivotal role in regulating the microenvironment of bone regeneration sites due to their unique ability to transform between M1 and M2 phenotypes, thus becoming the primary target for immunomodulation in current antioxidant bone scaffolds [107]. Specifically, upon activation, M1 macrophages secrete inflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin (IL)−1β, IL-6, and IL-23, which interfere with the normal function of osteoblasts, thereby affecting the formation and mineralization of bone matrix [108–111]. Conversely, M2 macrophages release anti-inflammatory cytokines and growth factors, such as transforming growth factor-β (TGF-β), bone morphogenetic protein-2 (BMP-2), IL-4, IL-10, and IL-13, which actively promote bone formation [110–112].

Currently, the anti-inflammatory and antioxidant properties inherent in certain natural polyphenols are being utilized to construct bone scaffolds that integrate immune modulation and antioxidant functions. These antioxidants not only protect BMSCs from oxidative stress but also directly promote the M2 polarization of macrophages. Recently, Li et al. have developed a proanthocyanidin optimizing chitosan scaffold (ChiO) with a microchannel structure using directional freeze-drying technology [113]. The scaffold was able to inhibit lipopolysaccharides (LPS)-induced M1 polarization of macrophages and collaboratively induced M2 polarization of macrophages through its directional pore structure and proanthocyanidin, thus achieving the regulation of the immune microenvironment. Furthermore, the proanthocyanidin in ChiO promoted better scaffold adhesion of BMSCs through polyphenol/protein adsorption, assisted in scavenging intracellular ROS induced by H_2O_2 in BMSCs, ultimately promoting osteogenic differentiation of BMSCs and accelerating the repair of rabbit skull defects. Similarly, Wang et al. constructed a hydrogel loaded with tannic acid (SFMA–LAP@TA), where the loaded tannic acid promoted M2 polarization of macrophages and alleviated oxidative stress in BMSCs caused by the conditioned medium of inflammatory macrophages (induced by LPS), thereby promoting the repair of rat skull defects [114].

The anti-inflammatory function of some antioxidants not only involves inhibiting pro-inflammatory signaling pathways (such as MAPK and NFκB) but also involves scavenging ROS in immune cells [115, 116]. Zhou et al. constructed a

polypyrrole–polydopamine–hydroxyapatite (PPy–PDA–HA) coating on Ti scaffolds via a layer-by-layer pulse electrodeposition method [117]. In this construct, electrons in PPy–PDA were captured by ROS, converting the catechin groups in PPy–PDA NPs into quinones and the dedoped state of PPy into the doped state, thus achieving antioxidant functions and effectively reducing ROS levels in RAW 264.7 cells. In addition, certain scaffolds averted M1 polarization due to excessive ROS accumulation by stimulating the intrinsic antioxidant systems within macrophages, consequently preventing the accumulation of inflammatory cytokines such as TNF-α and IL-1β that are detrimental to bone repair. In another study, Chen et al. have constructed a Se-doped mesoporous bioactive glass (Se–MBG) [118]. The presence of Se in the material can increase the expression of GPx4, a peroxide-scavenging enzyme, to eliminate ROS within macrophages, reduce mitochondrial swelling, and promote the recovery of mitochondrial oxidative phosphorylation, thus inducing M2 polarization of macrophages. In vivo, the Se–MBG scaffold significantly promoted the repair of critical-sized skull defects in rats, and this enhancement of bone regeneration was not observed in macrophage depletion models, further demonstrating the immune-modulatory bone regeneration effect of the Se–MBG scaffold. Similarly, Huang et al. incorporated selenium nanoparticles into poly (lactic acid–carbonate) (PDT) and β-tricalcium phosphate (β-TCP) to obtain PDT–TCP–SE scaffolds for the treatment of osteoporotic bone defects [119]. This scaffold was able to restore the decreased SOD and GSH activities in macrophages induced by erastin, a ferroptosis inducer, preventing ROS accumulation and promoting M2 polarization of macrophages. In addition, the PDT–TCP–SE scaffold could also restore the antioxidant capacity of BMSCs through the SIRT1/NRF2/GPx4 signaling pathway, alleviating the inhibition of osteogenic differentiation caused by erastin.

Antioxidant strategies for attenuating osteoclast formation

Osteoclasts, as a component of the hematopoietic monocyte–macrophage system, are primarily responsible for bone resorption and play a crucial role in the growth, repair, and remodeling of bone [120]. During bone regeneration, osteoclasts are often activated to clear damaged bone tissue through their resorptive function, thereby creating space for new bone growth. However, excessive oxidative stress, resulting from infections, diabetes, or osteoporosis, can lead to the hyperactivation of osteoclasts, thereby accelerating bone resorption and damage [121, 122]. Li et al. recently designed a manganese-containing β-tricalcium phosphate (Mn–TCP) bioceramic to inhibit osteoclast activation [123]. Specifically, Mn–TCP can effectively suppress oxidative stress and osteoclast formation induced by RANKL signaling by clearing ROS and activating the expression of antioxidant key signaling molecule NRF2 in macrophages. This ultimately promotes the repair of osteoporotic bone defects.

In patients with osteoporosis, excessive osteoclast activation is accompanied by the impairment of osteoblast precursor cell differentiation and osteoblast function due to oxidative stress [124]. Therefore, the development of antioxidant scaffolds that concurrently inhibit osteoclast activation and promote bone formation holds significant practical value. Recently, Chen et al. constructed a Ti implant (AHT–Ce/SrMOF) coated with a Ce/Sr/p-xylylenebisphosphonate metal–organic framework [125]. Ce

and Sr collectively imparted SOD and CAT-like activities to the AHT–Ce/SrMOF, which were utilized to scavenge mitochondrial ROS, thereby restoring mitochondrial autophagy and fusion. This implant ultimately led to the recovery of BMSC osteogenic differentiation functionality under osteoporotic conditions. Furthermore, the presence of p-xylylenebisphosphonate (PXBP) within the Ce/SrMOF also served to inhibit osteoclastogenesis. In vivo, the AHT–Ce/SrMOF augmented the osseointegration capability of titanium implants in an osteoporotic rat model. Considering that infection is a trigger for abnormal osteoclast activation, Huang et al. constructed a PATGP@PDA + Ag microsphere-based microscaffold by modifying aniline tetramer (AT) substituted polyphosphazene (PATGP) with polydopamine (PDA) and further loading it with silver nanoparticles (Ag NPs) [126]. Ag NPs significantly enhanced their antibacterial capabilities, while PATGP possessed ROS scavenging abilities due to its electron donor structure, which could be used to prevent BMSCs from oxidative stress interference. When applied to infective cranial bone defects, the microscaffold effectively reduced osteoclast activation caused by infection and accelerated bone repair. In another study, Xu et al. constructed a gallium (III)–phenolic coating composed of gallium and tannic acid on the surface of titanium implants [127]. The scaffold upregulated the expression of antioxidant genes Nqo1, Sod2, Sirt1, and Nrf2 in MC3T3-E1 cells, thereby restoring the osteogenic capacity of osteoblasts. In addition, gallium ions directly downregulated the expression of genes related to osteoclast differentiation (c-Fos, NFATC1) and bone resorption (CTSK, TRAP), inhibiting osteoclastogenesis. In vivo, the gallium (III)–phenolic coating also exhibited antibacterial properties through photothermal effects, ultimately promoting osseointegration of the implant.

Integrated antioxidant and anti-tumor therapeutics

Malignant bone tumors are invasive and destructive, which can directly erode and destroy bone structures, leading to bone dissolution and defects [128]. Therefore, many bone tumor patients who have undergone surgical treatment not only need to deal with the risk of tumor residuals, but also must face the challenges brought by bone defects. In recent years, scaffolds with both anti-tumor properties and bone regeneration capabilities have increasingly become the focus of research. In the study by Sistanipour et al., catechin-conjugated mesoporous hydroxyapatite nanoparticles (Cat@MHAP) were prepared on glass electrodes [129]. In vitro studies revealed that Cat@MHAP films inhibited the proliferation of osteosarcoma cells and scavenged ROS in cells, supporting the growth and osteogenic differentiation of MSCs, indicating its potential application in the treatment of bone defects after surgery for osteosarcoma patients. In another study, Gupta et al. constructed a composite scaffold consisting of doxorubicin-loaded and exosome-loaded nanocement, as well as a polymer film (PUAOC) containing *Cissus quadrangularis* (CQ) extract, for anti-osteosarcoma therapy and bone regeneration restoration [130]. In this study, doxorubicin effectively inhibited the proliferation of osteosarcoma cells, while exosomes and CQ scavenged ROS to protect MC3T3-E1 cells. In a tumor xenograft model, this composite scaffold successfully prevented tumor cell proliferation and promoted bone formation, contributing to the prevention of pathological fractures. These integrated scaffolds for anti-tumor and bone regeneration provide hope for bone regeneration after bone tumor surgery, yet such research is still

scarce. This may be due to the inherent contradiction between anti-tumor and bone regeneration strategies, as many current anti-tumor strategies rely on ROS-induced tumor cell death, which is contradictory to the low oxidative stress required for bone formation.

Smart antioxidant bone scaffolds

As an advanced material, smart biomaterials have exhibited tremendous potential and promising prospects in the field of bone tissue regeneration. These unique materials are capable of intelligently adjusting their physical and chemical properties in response to changes in the external environment, such as fluctuations in pH, temperature, or glucose concentration, thereby achieving precise controlled release of drugs, growth factors, or other bioactive substances [131, 132]. According to the studies on antioxidant bone scaffolds for bone regeneration published in recent years, it is evident that current smart bone scaffolds predominantly utilize hydrogel materials. This preference may be attributed to the relative ease with which reactive groups can be introduced into the constituents of hydrogels, thereby endowing the bone scaffolds with responsiveness to the bone microenvironment [133, 134]. Here, we will introduce several therapeutic strategies of smart antioxidant bone scaffolds currently used for bone regeneration based on existing studies.

The significant advantage of smart hydrogels in addressing bone defects lies in their ability to match the shape of bone injury sites. Recently, Li et al. designed an injectable thermosensitive hydrogel (Res@CHAp/Col I/PLEL) based on amphiphilic triblock copolymer poly(D,L-lactide)poly(ethylene glycol)–poly(D,L-lactide) (PDLLA–PEG–PDLLA, PLEL) for loading porous carbonate hydroxyapatite (CHAp) spheres and collagen I (Col I) [135]. This system existed as a homogeneous solution at room temperature, which can be injected to fill bone defects upon entering the body and subsequently transformed into a gel. Following gel formation, resveratrol (Res) and dexamethasone with strong antioxidant activity were released from CHAp spheres, effectively clearing ROS in macrophages and promoting their M2 polarization. In addition, Res@CHAp/Col I/PLEL can regulate angiogenesis and BMSCs osteogenic differentiation, promoting the repair of spongy bone defects.

The physicochemical microenvironment at the site of bone injury can serve as an effective signal to regulate the degradation properties of bone scaffolds, thereby achieving drug release that responds to the bone microenvironment [136]. In a recent study, the antioxidant enzyme catalase and PFC@PLGA/PPS co-loaded liposomes (CCP-L) were incorporated into hydrogels (CPP-L/GelMA) (Fig. 3A) [137]. CPP-L/GelMA not only triggered PFC@PLGA/PPS degradation via ROS to release oxygen, but also converted ROS into oxygen via catalase, thus achieving ROS scavenging and long-term oxygen supply. This scaffold effectively promoted osteogenic differentiation through regulation of NRF2–BMAL1–autophagy pathway, promoted angiogenesis, and inhibited osteoclast formation through ROS scavenging and improvement of hypoxic microenvironment, ultimately accelerating the repair of cranial defects (Fig. 3B–H). In diabetic bone defects, high glucose also acts as a degradation regulator of the bone scaffold and a substrate for cascade reactions. Recently, Liu et al. developed a Mn@Co_3O_4@Pt nanozyme with multi-enzyme-like activities, encapsulated within a hydrogel

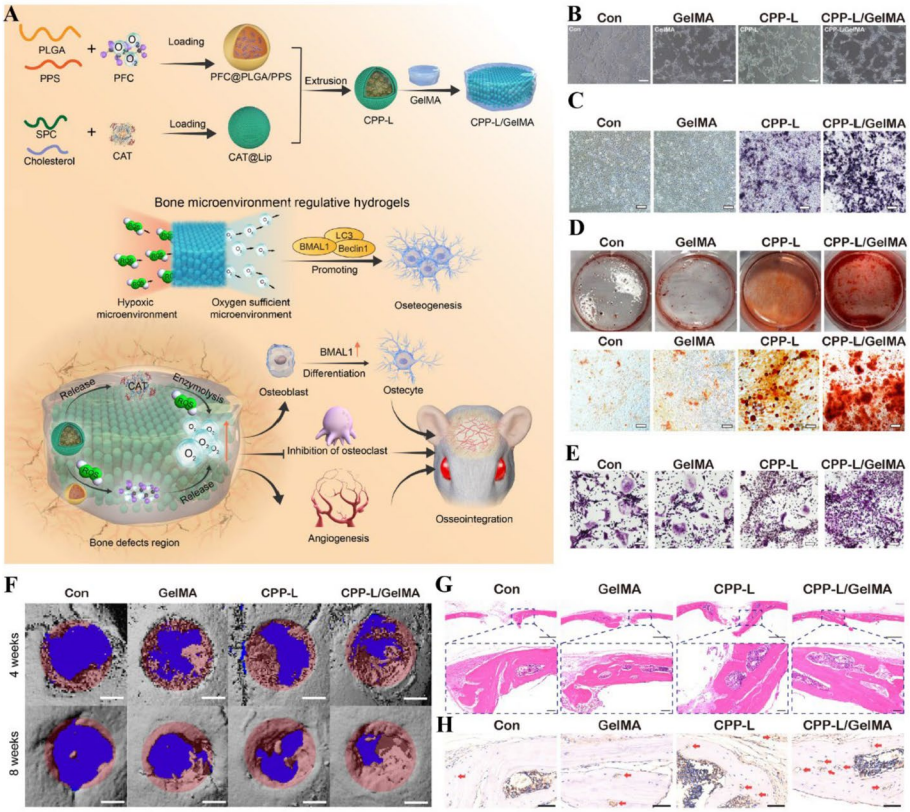

Fig. 3 Smart antioxidant bone scaffolds for bone regeneration. **A** Schematic illustration of CPP-L/GelMA scaffold for bone regeneration. **B** Tube formation images after treatment of HUVECs with different bone scaffolds. **C** ALP staining images of MC3T3-E1 cells after different treatments. **D** Alizarin red staining of MC3T3-E1 after different treatments. **E** TRAP staining of RAW 246.7 differentiated osteoblasts subjected to different treatments. **F** Micro-CT images of cranial defects after 4 and 8 weeks of treatment. **G** H&E staining of cranial defects after 8 weeks of treatment. **H** CD31 immunohistochemical staining of cranial defects after different treatments. Scale bars: 100 μm for **B**, **C**, **D** and **E** scale bars: 500 μm for F and the upper row of **G** scale bars: 50 μm for the second row of **G** and **H**. Adapted from [137], Elsevier, 2023

composed of poly(vinyl alcohol) (PVA) and phenyl boric acid-modified sodium alginate (Alg–PBA) [138]. When applied to diabetic bone defects, the hydrogel released Mn@Co_3O_4@Pt in a glucose-responsive manner, catalyzing glucose and superoxide anion to produce H_2O_2 through glucose oxidase (GOx)-like activity and SOD-like activity, respectively. Subsequently, H_2O_2 was further catalyzed to oxygen via CAT-like activity, achieving dual regulation of hyperglycemia and ROS in the local bone defect area, thereby providing a favorable microenvironment for bone regeneration.

Compared to the microenvironment-responsive drug delivery systems based on dynamic chemical bonds, the antioxidant scaffolds responsive to ultrasound exhibited a more proactive character due to their capability of remotely controlling drug release [139]. Recently, RES@poly(lactic–co-glycolic acid) nanobubbles (PLGA NBs) were encapsulated within GelMA/HAMA hydrogels to obtain UCE hydrogels [140]. Under ultrasound induction, UCE hydrogel released resveratrol, effectively inhibiting the secretion of inflammatory factors such as TNF-α and IL-1β in macrophages by scavenging ROS and inhibiting the phosphorylation of the NF-κB pathway, thus achieving the control of acute immune peaks within 24–48 h after bone injury. In vivo,

UCE hydrogel effectively regulated the spatial–temporal bone immune disorder and promoted the repair of skull defects.

Light-responsive scaffolds are gaining attention in the field of bone tissue engineering due to their non-contact and controllable advantages [141]. The application of light-responsive scaffolds in tissue regeneration typically involves photothermal effects or photodynamic therapy, which induce bacterial ROS accumulation and death to exert antibacterial effects [142]. In addition, the photothermal effect can modulate the release characteristics of antioxidants by altering the temperature, thereby increasing the efficiency of drug utilization [143]. However, there is an inherent contradiction between ROS-based antibacterial therapies and antioxidant therapies, resulting in a lack of synergistic applications between phototherapy and antioxidant therapies. In recent years, with the continuous exploration of mild photothermal therapy, some studies have found that bacteria are sensitive to mild photothermal therapy at 42–43 °C, whereas it is safe for bone repair-related cells in this temperature range, and even have osteogenic differentiation-promoting and anti-inflammatory functions [141, 144]. Recently, Ding et al. constructed TA–D-Tyr NPs through the self-assembly of D-tyrosine (D-Tyr) and tannic acid, and created a hydrogel coating loaded with TA–D-Tyr NPs on the surface of titanium (Ti–G–TA–D-Tyr) [145]. By utilizing the synergistic effect of the mild photothermal effect of 43 °C, the biofilm solubilizing properties of D-Tyr, and the antibacterial effect of tannic acid, Ti–G–TA–D-Tyr demonstrated enhanced anti-biofilm and anti-planktonic bacterial activity, exhibiting excellent osteointegration performance in infected bone defects. In another study, Zhu et al. constructed a dynamic GAD/MC hydrogel composed of copper-containing $Ti_3C_2T_x$ MXene nanosheets, GelMA, and alginate–graft–dopamine, and elucidated the synergistic promotion of bone regeneration through mild photothermal therapy and antioxidant therapy [146]. Specifically, the phenolic–quinone groups of alginate–graft–dopamine and the electron transport capabilities of Ti_3C_2 MXene synergistically exhibited potent ROS scavenging abilities. In addition, mild photothermal effects (at 42 °C) further enhanced the antioxidant effect of this system. In diabetic rats, mild photothermal therapy could assist antioxidant therapy, demonstrating enhanced M2 polarization of macrophages, osteogenic differentiation, and angiogenic regulation under inflammatory conditions, effectively promoting cranial bone repair.

Conclusions and future perspectives

In this study, we first elucidated the mechanisms by which oxidative stress impedes bone repair. Subsequently, we categorized and summarized the commonly used bone scaffolds and antioxidants to enhance the understanding of antioxidant scaffolds. In addition, we review the progress in the application of antioxidant bone scaffolds, focusing on their regulatory strategies in cellular functions. Finally, due to the rapid development of smart biomaterials in recent years, we also highlighted recent progress and representative strategies in the application of microenvironment-responsive, ultrasound-responsive, and light-responsive antioxidant scaffolds for bone regeneration. In conclusion, advancements in antioxidant bone scaffolds have expanded therapeutic options for promoting bone regeneration.

However, it is worth noting that these emerging antioxidant bone scaffolds are currently still in the laboratory research stage. Although they have shown great potential in bone regeneration, there are still several challenges to be addressed before clinical application:

1. Bone repair is a coordinated process involving various cells. However, research on antioxidant scaffolds mainly focuses on their biological effects on osteoblast lineage, endothelial cells, macrophages, and osteoclasts, while studies on how antioxidant actions affect neural regeneration or other immune cells (such as T cells and neutrophils) are still lacking.
2. The current material selection for metal scaffolds still mainly relies on titanium. However, research on the antioxidant performance of degradable multifunctional metal scaffolds (such as magnesium, zinc, iron, strontium, manganese, calcium, and their alloys) remains scarce. In addition, when studying degradable antioxidant bone scaffolds, the matching of scaffold degradation rate with bone regeneration rate needs to be considered.
3. The microstructural characteristics of scaffolds, such as morphology and pore, significantly influence cellular behavior. While pursuing antioxidant performance, it is necessary to ensure that scaffold design supports cell growth and migration to enhance its efficacy in bone regeneration therapy.
4. When antioxidants are loaded into scaffolds, the scaffold and antioxidants should be regarded as an integrated whole, and their mechanisms of action should be comprehensively analyzed, rather than focusing only on the drug itself. Such comprehensive analysis helps to better understand the interaction between scaffolds and drugs and optimize their therapeutic effects in promoting bone regeneration.
5. With the rapid development of nanotechnology, nanomaterials show great potential in the fields of biosensing and molecular detection. However, there are few reports in current research on integrating nanomaterials with antioxidant scaffolds to achieve integrated diagnosis and treatment.
6. There is a lack of reports on the toxicity of antioxidant scaffolds, which may be attributed to publication bias. Moreover, the optimization processes designed to ensure the biocompatibility of antioxidant scaffolds are often insufficiently detailed, thereby limiting their capacity to provide meaningful guidance for future research. On the other hand, further studies are required to investigate the long-term biocompatibility of these scaffolds, ensuring their safety and reliability for clinical applications.
7. Before transitioning antioxidant scaffolds from the laboratory research stage to clinical application, it is necessary to standardize their production processes to ensure the consistency of quality and performance in each batch of scaffolds. At the same time, ways to reduce costs need to be actively explored to facilitate the widespread use of these stents in clinical practice.

In summary, antioxidant bone scaffolds have shown extraordinary potential in the field of bone regeneration. With continued research and exploration, antioxidant

bone scaffolds are poised to become safer and more efficient therapeutic tools for bone regeneration, thus ushering in a new era of bone defect treatment.

Abbreviations

BMSCs	Bone-marrow-derived mesenchymal stem cells
ROS	Reactive oxygen species
Ti	Titanium
SOD	Superoxide dismutase
CAT	Catalase
GPx	Glutathione peroxidase
HO-1	Heme oxygenase-1
PCL	Polycaprolactone
OD	Oxidized dextran
MHA	3-Aminopropyltriethoxysilane and nano-hydroxyapatite doped micro-arc oxidation
PLA	Polylactide
PEEK	Polyetheretherketone
TPG	Tea polyphenol-reduced graphene
ChSMA	Methacryloylated chondroitin sulfate
GelMA	Gelatin methacrylate
NPs	Nanoparticles
POM	Molybdenum-based polyoxometalate
GSH	Glutathione
GelMA–g-GSH	Glutathione-grafted gelatin methacrylate hydrogel
OVX-BMSCs	Bone-marrow-derived mesenchymal stem cells isolated from ovariectomized rats
SF/CPC	Silk fibroin/calcium phosphate cement
Se@SF/CPC	Na_2SeO_3-doped silk fibroin/calcium phosphate cement scaffold
SF@MT	Silk fibroin scaffold loaded with melatonin
MT@PLGA	Melatonin-loaded polylactic–co-glycolic acid
PCL/β-TCP	Polycaprolactone/β-Tricalcium phosphate
VEGF	Vascular endothelial growth factor
Emcn	Endomucin
HUVECs	Human umbilical vein endothelial cells
TNF-α	Tumor necrosis factor-α
IL	Interleukin
TGF-β	Transforming growth factor-β
BMP-2	Bone morphogenetic protein-2
ChiO	Proanthocyanidin optimizing chitosan scaffold
LPS	Lipopolysaccharides
PPy–PDA–HA	Polypyrrole–polydopamine–hydroxyapatite
Se–MBG	Se-doped mesoporous bioactive glass
PDT	Poly (lactic acid–carbonate)
Mn–TCP	Manganese-containing β-tricalcium phosphate
PXBP	P-xylylenebisphosphonate
AT	Aniline tetramer
PDA	Polydopamine
Ag NPs	Silver nanoparticles
Cat@MHAP	Catechin-conjugated mesoporous hydroxyapatite nanoparticles
CQ	Cissus quadrangularis
CHAp	Porous carbonate hydroxyapatite
Col I	Collagen I
Res	Resveratrol
PVA	Poly(vinyl alcohol)
Alg–PBA	Phenyl boric acid-modified sodium alginate
Gox	Glucose oxidase
D-Tyr	D-tyrosine

Acknowledgements
Figure 1 was created by Figdraw (www.figdraw.com).

Author contributions
H.L. and Z.Z. conceived the review and drafted the manuscript. J.L. and H.W. revised the manuscript. All authors contributed to the article and approved the submitted version.

Funding
This study was not funded by any project funding.

Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 9 November 2024 Accepted: 24 March 2025
Published online: 08 April 2025

References

1. Zhao D, Zhu T, Li J, Cui L, Zhang Z, Zhuang X, Ding J. Poly(lactic-co-glycolic acid)-based composite bone-substitute materials. Bioact Mater. 2021;6:346–60.
2. Dalfino S, Savadori P, Piazzoni M, Connelly ST, Giannì AB, Del Fabbro M, Tartaglia GM, Moroni L. Regeneration of critical-sized mandibular defects using 3D-printed composite scaffolds: a quantitative evaluation of new bone formation in in vivo studies. Adv Healthc Mater. 2023;12: e2300128.
3. Zhang Z, Xue H, Xiong Y, Geng Y, Panayi AC, Knoedler S, Dai G, Shahbazi MA, Mi B, Liu G. Copper incorporated biomaterial-based technologies for multifunctional wound repair. Theranostics. 2024;14:547–70.
4. Zhu G, Zhang T, Chen M, Yao K, Huang X, Zhang B, Li Y, Liu J, Wang Y, Zhao Z. Bone physiological microenvironment and healing mechanism: basis for future bone-tissue engineering scaffolds. Bioact Mater. 2021;6:4110–40.
5. Feng P, He R, Gu Y, Yang F, Pan H, Shuai C. Construction of antibacterial bone implants and their application in bone regeneration. Mater Horiz. 2024;11:590–625.
6. Liu J, Yang L, Liu K, Gao F. Hydrogel scaffolds in bone regeneration: their promising roles in angiogenesis. Front Pharmacol. 2023;14:1050954.
7. Roseti L, Parisi V, Petretta M, Cavallo C, Desando G, Bartolotti I, Grigolo B. Scaffolds for bone tissue engineering: state of the art and new perspectives. Mater Sci Eng C Mater Biol Appl. 2017;78:1246–62.
8. Ma Z, Guo X, Zhang J, Jiang Q, Liang W, Meng W, Chen S, Zhu Y, Ye C, Jia K. Evaluation of safety and efficacy of the bone marrow mesenchymal stem cell and gelatin-nano-hydroxyapatite combination in canine femoral defect repair. Front Vet Sci. 2023;10:1162407.
9. Hou X, Zhang L, Zhou Z, Luo X, Wang T, Zhao X, Lu B, Chen F, Zheng L. Calcium phosphate-based biomaterials for bone repair. J Funct Biomater. 2022;13:187.
10. Jiang M, Pan Y, Liu Y, Dai K, Zhang Q, Wang J. Effect of sulfated chitosan hydrogel on vascularization and osteogenesis. Carbohydr Polym. 2022;281: 119059.
11. Liu J, Han X, Zhang T, Tian K, Li Z, Luo F. Reactive oxygen species (ROS) scavenging biomaterials for anti-inflammatory diseases: from mechanism to therapy. J Hematol Oncol. 2023;16:116.
12. Lao A, Wu J, Li D, Shen A, Li Y, Zhuang Y, Lin K, Wu J, Liu J. Functionalized metal-organic framework-modified hydrogel that breaks the vicious cycle of inflammation and ROS for repairing of diabetic bone defects. Small. 2023;19: e2206919.
13. Gao X, Al-Baadani MA, Wu M, Tong N, Shen X, Ding X, Liu J. Study on the local anti-osteoporosis effect of polaprezinc-loaded antioxidant electrospun membrane. Int J Nanomedicine. 2022;17:17–29.
14. Dulany K, Hepburn K, Goins A, Allen JB. In vitro and in vivo biocompatibility assessment of free radical scavenging nanocomposite scaffolds for bone tissue regeneration. J Biomed Mater Res A. 2020;108:301–15.
15. Karimi-Soflou R, Mohseni-Vadeghani E, Karkhaneh A. Controlled release of resveratrol from a composite nanofibrous scaffold: effect of resveratrol on antioxidant activity and osteogenic differentiation. J Biomed Mater Res A. 2022;110:21–30.
16. Unalan I, Fuggerer T, Slavik B, Buettner A, Boccaccini AR. Antibacterial and antioxidant activity of cinnamon essential oil-laden 45S5 bioactive glass/soy protein composite scaffolds for the treatment of bone infections and oxidative stress. Mater Sci Eng C Mater Biol Appl. 2021;128: 112320.
17. Gao Z, Song Z, Guo R, Zhang M, Wu J, Pan M, Du Q, He Y, Wang X, Gao L, Jin Y, Jing Z, Zheng J. Mn single-atom nanozyme functionalized 3d-printed bioceramic scaffolds for enhanced antibacterial activity and bone regeneration. Adv Healthc Mater. 2024;13: e2303182.
18. Li F, Li J, Song X, Sun T, Mi L, Liu J, Xia X, Bai N, Li X. Alginate/gelatin hydrogel scaffold containing nCeO(2) as a potential osteogenic nanomaterial for bone tissue engineering. Int J Nanomed. 2022;17:6561–78.
19. Gai Y, Yin Y, Guan L, Zhang S, Chen J, Yang J, Zhou H, Li J. Rational design of bioactive materials for bone hemostasis and defect repair. Cyborg Bionic Syst. 2023;4:0058.
20. Qiao W, Pan D, Zheng Y, Wu S, Liu X, Chen Z, Wan M, Feng S, Cheung KMC, Yeung KWK, Cao X. Divalent metal cations stimulate skeleton interoception for new bone formation in mouse injury models. Nat Commun. 2022;13:535.
21. Chen S, Liang H, Ji Y, Kou H, Zhang C, Shang G, Shang C, Song Z, Yang L, Liu L, Wang Y, Liu H. Curcumin modulates the crosstalk between macrophages and bone mesenchymal stem cells to ameliorate osteogenesis. Front Cell Dev Biol. 2021;9: 634650.
22. Schindeler A, McDonald MM, Bokko P, Little DG. Bone remodeling during fracture repair: The cellular picture. Semin Cell Dev Biol. 2008;19:459–66.

23. Huang HM, Han CS, Cui SJ, Zhou YK, Xin TY, Zhang T, Zhu SB, Zhou YH, Yang RL. Mechanical force-promoted osteoclastic differentiation via periodontal ligament stem cell exosomal protein ANXA3. Stem Cell Rep. 2022;17:1842–58.
24. Wang W, Yuan C, Geng T, Liu Y, Zhu S, Zhang C, Liu Z, Wang P. EphrinB2 overexpression enhances osteogenic differentiation of dental pulp stem cells partially through ephrinB2-mediated reverse signaling. Stem Cell Res Ther. 2020;11:40.
25. Jörg DJ, Fuertinger DH, Cherif A, Bushinsky DA, Mermelstein A, Raimann JG, Kotanko P. Modeling osteoporosis to design and optimize pharmacological therapies comprising multiple drug types. Elife. 2022;11:9.
26. Mármol I, Sánchez-de-Diego C, Jiménez-Moreno N, Ancín-Azpilicueta C, Rodríguez-Yoldi MJ. Therapeutic applications of rose hips from different rosa species. Int J Mol Sci. 2017;18:1137.
27. Hao YM, He DW, Gao Y, Fang LN, Zhang PP, Lu K, Lu RZ, Li C. Association of hydrogen sulfide with femoral bone mineral density in osteoporosis patients: a preliminary study. Med Sci Monit. 2021;27: e929389.
28. Wu P, Shen L, Liu HF, Zou XH, Zhao J, Huang Y, Zhu YF, Li ZY, Xu C, Luo LH, Luo ZQ, Wu MH, Cai L, Li XK, Wang ZG. The marriage of immunomodulatory, angiogenic, and osteogenic capabilities in a piezoelectric hydrogel tissue engineering scaffold for military medicine. Mil Med Res. 2023;10:35.
29. Majrashi M, Kotowska A, Scurr D, Hicks JM, Ghaemmaghami A, Yang J. Sustained release of dexamethasone from 3D-printed scaffolds modulates macrophage activation and enhances osteogenic differentiation. ACS Appl Mater Interfaces. 2023;15:56623–38.
30. Liu PL, Diao JY, Wang Q, Liu H, Zhang Y, Liang JQ, Zhang F, Liang XJ, Zhao HM. Cartilage damage pathological characteristics of diabetic neuropathic osteoarthropathy. Anal Cell Pathol. 2023;2023:7573165.
31. Brassolatti P, Castro CA, Santos HLD, Simões IT, Almeida-Lopes L, Silva JVD, Duarte FO, Luna GLF, Beck WR, Bossini PS, Anibal FF. Systemic and local inflammatory response after implantation of biomaterial in critical bone injuries. Acta Cir Bras. 2023;38: e383823.
32. Hu XF, Wang L, Lu YZ, Xiang G, Wu ZX, Yan YB, Zhang Y, Zhao X, Zang Y, Shi L, Lei W, Feng YF. Adiponectin improves the osteointegration of titanium implant under diabetic conditions by reversing mitochondrial dysfunction via the AMPK pathway in vivo and in vitro. Acta Biomater. 2017;61:233–48.
33. Ellermann E, Meyer N, Cameron RE, Best SM. In vitro angiogenesis in response to biomaterial properties for bone tissue engineering: a review of the state of the art. Regen Biomater. 2023;10:rbad027.
34. Hsieh KH, Hsu HC, Wu SC, Shih YC, Yang HW, Ho WF. Effect of hydrothermal and vapor thermal treatments on apatite inductivity of titanate nanotubes on anodized Ti-5Nb-5Mo surface. Nanomaterials. 2023;13:1296.
35. Jung O, Smeets R, Hartjen P, Schnettler R, Feyerabend F, Klein M, Wegner N, Walther F, Stangier D, Henningsen A, Rendenbach C, Heiland M, Barbeck M, Kopp A. Improved in vitro test procedure for full assessment of the cytocompatibility of degradable magnesium based on ISO 10993–5/-12. Int J Mol Sci. 2019;20:1.
36. Parai R, Bandyopadhyay-Ghosh S. Engineered bio-nanocomposite magnesium scaffold for bone tissue regeneration. J Mech Behav Biomed Mater. 2019;96:45–52.
37. Elmosallamy MAF, Hashem HA, Abdalmoez FF. New solid-state membrane and coated wire potentiometric sensors for the determination of Zn(II) ions based on nanoparticles. Anal Bioanal Chem. 2022;414:8277–87.
38. He J, Fang J, Wei P, Li Y, Guo H, Mei Q, Ren F. Cancellous bone-like porous Fe@Zn scaffolds with core-shell-structured skeletons for biodegradable bone implants. Acta Biomater. 2021;121:665–81.
39. Wei S, Ma JX, Xu L, Gu XS, Ma XL. Biodegradable materials for bone defect repair. Mil Med Res. 2020;7:54.
40. Chen Y, Gan W, Cheng Z, Zhang A, Shi P, Zhang Y. Plant molecules reinforce bone repair: Novel insights into phenol-modified bone tissue engineering scaffolds for the treatment of bone defects. Mater Today Bio. 2024;24: 100920.
41. Yun C, Kim SH, Kim KM, Yang MH, Byun MR, Kim JH, Kwon D, Pham HTM, Kim HS, Kim JH, Jung YS. Advantages of using 3D spheroid culture systems in toxicological and pharmacological assessment for osteogenesis research. Int J Mol Sci. 2024;25:2512.
42. Huang D, Zhao F, Gao W, Chen X, Guo Z, Zhang W. Strontium-substituted sub-micron bioactive glasses inhibit ostoclastogenesis through suppression of RANKL-induced signaling pathway. Regen Biomater. 2020;7:303–11.
43. Yang Y, Kulkarni A, Soraru GD, Pearce JM, Motta A. 3D printed SiOC(N) ceramic scaffolds for bone tissue regeneration: improved osteogenic differentiation of human bone marrow-derived mesenchymal stem cells. Int J Mol Sci. 2021;22:2.
44. Mirzaali MJ, Moosabeiki V, Rajaai SM, Zhou J, Zadpoor AA. Additive manufacturing of biomaterials-design principles and their implementation. Materials. 2022;15:5547.
45. Sheikh Z, Najeeb S, Khurshid Z, Verma V, Rashid H, Glogauer M. Biodegradable materials for bone repair and tissue engineering applications. Materials. 2015;8:5744–94.
46. Lesage C, Lafont M, Guihard P, Weiss P, Guicheux J, Delplace V. Material-assisted strategies for osteochondral defect repair. Adv Sci. 2022;9:e2200050.
47. Mohammed AA, Li S, Sang T, Jones JR, Pinna A. Nanocomposite hydrogels with polymer grafted silica nanoparticles, using glucose oxidase. Gels. 2023;9:486.
48. Zhou J, Vijayavenkataraman S. A 'relay'-type drug-eluting nerve guide conduit: computational fluid dynamics modeling of the drug eluting efficiency of various drug release systems. Pharmaceutics. 2022;14:230.
49. McMahan S, Taylor A, Copeland KM, Pan Z, Liao J, Hong Y. Current advances in biodegradable synthetic polymer based cardiac patches. J Biomed Mater Res A. 2020;108:972–83.
50. Chang S, Wang S, Liu Z, Wang X. Advances of stimulus-responsive hydrogels for bone defects repair in tissue engineering. Gels. 2022;8:389.
51. Han F, Wang J, Ding L, Hu Y, Li W, Yuan Z, Guo Q, Zhu C, Yu L, Wang H, Zhao Z, Jia L, Li J, Yu Y, Zhang W, Chu G, Chen S, Li B. Tissue engineering and regenerative medicine: achievements, future, and sustainability in Asia. Front Bioeng Biotechnol. 2020;8:83.
52. Aslam Khan MU, Mehboob H, Abd Razak SI, Yahya MY, Mohd Yusof AH, Ramlee MH, Sahaya Anand TJ, Hassan R, Aziz A, Amin R. Development of polymeric nanocomposite (xyloglucan-co-methacrylic acid/hydroxyapatite/

SiO(2)) Scaffold for bone tissue engineering applications-in-vitro antibacterial. Cytotox Cell Cult Evaluat Polym. 2020;12:1238.
53. Vahedi S, Aghdam RM, Sohi MH, Rezayan AH. Characteristics of electrospun chitosan/carbon nanotube coatings deposited on AZ31 magnesium alloy. J Mater Sci Mater Med. 2023;34:8.
54. Smith IO, Liu XH, Smith LA, Ma PX. Nanostructured polymer scaffolds for tissue engineering and regenerative medicine. Wiley Interdiscip Rev Nanomed Nanobiotechnol. 2009;1:226–36.
55. Enderami SE, Shafiei SS, Shamsara M, Enderami SE, Rostamian TA. Evaluation of osteogenic differentiation of bone marrow-derived mesenchymal stem cell on highly porous polycaprolactone scaffold reinforced with layered double hydroxides nanoclay. Front Bioeng Biotechnol. 2022;10: 805969.
56. Battogtokh G, Choi YS, Kang DS, Park SJ, Shim MS, Huh KM, Cho YY, Lee JY, Lee HS, Kang HC. Mitochondria-targeting drug conjugates for cytotoxic, anti-oxidizing and sensing purposes: current strategies and future perspectives. Acta Pharm Sin B. 2018;8:862–80.
57. Singh N, Yadav SS. A review on health benefits of phenolics derived from dietary spices. Curr Res Food Sci. 2022;5:1508–23.
58. Zhang L, Yao L, Zhao F, Yu A, Zhou Y, Wen Q, Wang J, Zheng T, Chen P. Protein and peptide-based nanotechnology for enhancing stability, bioactivity, and delivery of anthocyanins. Adv Healthc Mater. 2023;12: e2300473.
59. Karunarathne W, Molagoda IMN, Lee KT, Choi YH, Jin CY, Kim GY. Anthocyanin-enriched polyphenols from Hibiscus syriacus L. (Malvaceae) exert anti-osteoporosis effects by inhibiting GSK-3β and subsequently activating β-catenin. Phytomedicine. 2021;91:153721.
60. Pham TH, Kim EN, Trang NM, Jeong GS. Gallic acid induces osteoblast differentiation and alleviates inflammatory response through GPR35/GSK3β/β-catenin signaling pathway in human periodontal ligament cells. J Periodontal Res. 2024;59:204–19.
61. Zhang W, Zeng QM, Tang RC. Gallic acid functionalized polylysine for endowing cotton fiber with antibacterial, antioxidant, and drug delivery properties. Int J Biol Macromol. 2022;216:65–74.
62. Zhang X, Xu L, Chen X, Zhou X, Cao L. Acacetin alleviates neuroinflammation and oxidative stress injury via the Nrf2/HO-1 pathway in a mouse model of spinal cord injury. Transl Neurosci. 2022;13:483–94.
63. Li J, Ma J, Sun H, Yu M, Wang H, Meng Q, Li Z, Liu D, Bai J, Liu G, Xing X, Han F, Li B. Transformation of arginine into zero-dimensional nanomaterial endows the material with antibacterial and osteoinductive activity. Sci Adv. 2023;9:eadf8645.
64. Zhang X, Peng F, Wang D. MOFs and MOF-derived materials for antibacterial application. J Funct Biomater. 2022;13:215.
65. Jiang B, Fang L, Wu K, Yan X, Fan K. Ferritins as natural and artificial nanozymes for theranostics. Theranostics. 2020;10:687–706.
66. Chen Q, Nan Y, Yang Y, Xiao Z, Liu M, Huang J, Xiang Y, Long X, Zhao T, Wang X, Huang Q, Ai K. Nanodrugs alleviate acute kidney injury: manipulate RONS at kidney. Bioact Mater. 2023;22:141–67.
67. Chen Y, Tian Q, Wang H, Ma R, Han R, Wang Y, Ge H, Ren Y, Yang R, Yang H, Chen Y, Duan X, Zhang L, Gao J, Gao L, Yan X, Qin Y. A manganese-based metal-organic framework as a cold-adapted nanozyme. Adv Mater. 2024;36: e2206421.
68. Xu J, Bao G, Jia B, Wang M, Wen P, Kan T, Zhang S, Liu A, Tang H, Yang H, Yue B, Dai K, Zheng Y, Qu X. An adaptive biodegradable zinc alloy with bidirectional regulation of bone homeostasis for treating fractures and aged bone defects. Bioact Mater. 2024;38:207–24.
69. Sheng N, Xing F, Wang J, Zhang QY, Nie R, Li-Ling J, Duan X, Xie HQ. Recent progress in bone-repair strategies in diabetic conditions. Mater Today Bio. 2023;23: 100835.
70. Corrado A, Cici D, Rotondo C, Maruotti N, Cantatore FP. Molecular basis of bone aging. Int J Mol Sci. 2020;21:3679.
71. Jiang X, Wei J, Ding X, Zheng K, Zhou T, Shi J, Lai H, Qian S, Zhang X. From ROS scavenging to boosted osseointegration: cerium-containing mesoporous bioactive glass nanoparticles functionalized implants in diabetes. J Nanobiotechnology. 2024;22:639.
72. Zhu Y, Shi Z, Pang Y, Zhou Y. Deferoxamine-loaded gelatin methacryloyl hydrogel endue 3D-printed PGCL-hydroxyapatite scaffold with angiogenesis, anti-oxidative and immunoregulatory capacities for facilitating bone healing. Int J Biol Macromol. 2025;295: 139509.
73. Chen T, Wu Z, Hou Q, Mei Y, Yang K, Xu J, Wang L. The dual angiogenesis effects via Nrf2/HO-1 signaling pathway of melatonin nanocomposite scaffold on promoting diabetic bone defect repair. Int J Nanomedicine. 2024;19:2709–32.
74. Wu T, Yu S, Chen D, Wang Y. Bionic Design, Materials and Performance of Bone Tissue Scaffolds. Materials (Basel). 2017;10.
75. Koushik TM, Miller CM, Antunes E. Bone tissue engineering scaffolds: function of multi-material hierarchically structured Scaffolds. Adv Healthc Mater. 2023;12: e2202766.
76. Chen M, Li M, Wei Y, Xue C, Chen M, Fei Y, Tan L, Luo Z, Cai K, Hu Y. ROS-activatable biomimetic interface mediates in-situ bioenergetic remodeling of osteogenic cells for osteoporotic bone repair. Biomaterials. 2022;291: 121878.
77. Huang J, Li R, Yang J, Cai M, Lee Y, Wang A, Cheng B, Wang Y. Bioadaptation of implants to In vitro and In vivo oxidative stress pathological conditions via nanotopography-induced FoxO1 signaling pathways to enhance Osteoimmunal regeneration. Bioact Mater. 2021;6:3164–76.
78. Jalali H, Salemian M, Nabiuni M, Kouchesfehani HM, Bardei LK, Gregory C. Fabrication and application of salicin-polycaprolactone 3D-printed scaffold in the healing of femur bone defects. Biomed Mater. 2024;19: 035020.
79. Bai Z, Hu K, Shou Z, Zhou H, Yu J, Meng H, Chen L, Yu T, Lu R, Li N, Chen C. Engineering a mucin coating to promote osteogenic differentiation of BMSCs in vitro and bone formation in vivo through the Wnt/β-catenin pathway. Colloids Surf B Biointerfaces. 2023;221: 113000.
80. Shi Z, Yang F, Hu Y, Pang Q, Shi L, Du T, Cao Y, Song B, Yu X, Cao Z, Ye Z, Liu C, Yu R, Chen X, Zhu Y, Pang Q. An oxidized dextran-composite self-healing coated magnesium scaffold reduces apoptosis to induce bone regeneration. Carbohydr Polym. 2024;327: 121666.

81. Guo J, Yang X, Chen J, Wang C, Kang Y, Jiang T, Chen M, Li W, Zhou C, Chen Z. Accelerated Bone regeneration by an astaxanthin-modified antioxidant aerogel through relieving oxidative stress via the NRF2 signaling pathway. ACS Biomater Sci Eng. 2022;8:4524–34.
82. Tao ZS, Wang HS, Li TL, Wei S. Silibinin-modified Hydroxyapatite coating promotes the osseointegration of titanium rods by activation SIRT1/SOD2 signaling pathway in diabetic rats. J Mater Sci Mater Med. 2022;33:62.
83. Zhang J, Wang T, Zhang H, Deng H, Kuang T, Shen Z, Gu Z. Biomimetic polyphenolic scaffolds with antioxidative abilities for improved bone regeneration. ACS Appl Bio Mater. 2023;6:4586–91.
84. Fu LM, Wang S, Zhang N, Lin YJ, Zhang SH, Mao YJ, Zhou PH. Breaking the vicious cycle of cellular senescence and ROS via a mitochondrial-targeted hydrogel for aged bone regeneration. Chem Eng J. 2025;503:17.
85. Ou ZX, Wei JY, Lei J, Wu D, Tong BD, Liang HZ, Zhu DC, Wang HC, Zhou XY, Xu HP, Du Z, Du YF, Tan L, Yang C, Feng XB. Biodegradable Janus sonozyme with continuous reactive oxygen species regulation for treating infected critical-sized bone defects. Nat Commun. 2024;15:23.
86. Li KC, Chang YH, Hsu MN, Lo SC, Li WH, Hu YC. Baculovirus-mediated miR-214 knockdown shifts osteoporotic ASCs differentiation and improves osteoporotic bone defects repair. Sci Rep. 2017;7:16225.
87. Verbruggen SW. Role of the osteocyte in bone metastasis—the importance of networking. J Bone Oncol. 2024;44: 100526.
88. Turner CH, Warden SJ, Bellido T, Plotkin LI, Kumar N, Jasiuk I, Danzig J, Robling AG. Mechanobiology of the skeleton. Sci Signal. 2009;2:pt3.
89. Wang J, Zhang Y, Cao J, Wang Y, Anwar N, Zhang Z, Zhang D, Ma Y, Xiao Y, Xiao L, Wang X. The role of autophagy in bone metabolism and clinical significance. Autophagy. 2023;19:2409–27.
90. Tomić N, Stevanović MM, Filipović N, Ganić T, Nikolić B, Gajić I, Ćulafić DM. Resveratrol/Selenium Nanocomposite with Antioxidative and Antibacterial Properties. Nanomaterials. 2024;14:368.
91. Guo Q, Yang S, Ni G, Ji J, Luo M, Du W. The preparation and effects of organic-inorganic antioxidative biomaterials for bone repair. Biomedicines. 2023;12:70.
92. Tan X, Wu J, Wang R, Wang C, Sun Y, Wang Z, Ye L. PgC(3)Mg metal-organic cages functionalized hydrogels with enhanced bioactive and ROS scavenging capabilities for accelerated bone regeneration. J Mater Chem B. 2022;10:5375–87.
93. Wang S, Yao Z, Zhang X, Li J, Huang C, Ouyang Y, Qian Y, Fan C. Energy-Supporting Enzyme-Mimic Nanoscaffold Facilitates Tendon Regeneration Based on a Mitochondrial Protection and Microenvironment Remodeling Strategy. Adv Sci. 2022;9:e2202542.
94. Zhang M, Zhai X, Ma T, Huang Y, Jin M, Yang H, Fu H, Zhang S, Sun T, Jin X, Du Y, Yan CH. Sequential therapy for bone regeneration by cerium oxide-reinforced 3D-printed bioactive glass scaffolds. ACS Nano. 2023;17:4433–44.
95. Liao X, Shen M, Li T, Feng L, Lin Z, Shi G, Pei G, Cai X. Combined molybdenum gelatine methacrylate injectable nano-hydrogel effective against diabetic bone regeneration. Int J Nanomedicine. 2023;18:5925–42.
96. Zhou Q, Chen W, Gu C, Liu H, Hu X, Deng L, He W, Xu Y, Zhu X, Yang H, Chen X, He F, Liu T. Selenium-modified bone cement promotes osteoporotic bone defect repair in ovariectomized rats by restoring GPx1-mediated mitochondrial antioxidant functions. Regen Biomater. 2023;10:rbad011.
97. Das A, Nikhil A, Shiekh PA, Yadav B, Jagavelu K, Kumar A. Ameliorating impaired cardiac function in myocardial infarction using exosome-loaded gallic-acid-containing polyurethane scaffolds. Bioact Mater. 2024;33:324–40.
98. Wang L, Shen M, Hou Q, Wu Z, Xu J, Wang L. 3D printing of reduced glutathione grafted gelatine methacrylate hydrogel scaffold promotes diabetic bone regeneration by activating PI3K/Akt signaling pathway. Int J Biol Macromol. 2022;222:1175–91.
99. Liu J, Gao Z, Liu X. Mitochondrial dysfunction and therapeutic perspectives in osteoporosis. Front Endocrinol. 2024;15:1325317.
100. Gu C, Zhou Q, Hu X, Ge X, Hou M, Wang W, Liu H, Shi Q, Xu Y, Zhu X, Yang H, Chen X, Liu T, He F. Melatonin rescues the mitochondrial function of bone marrow-derived mesenchymal stem cells and improves the repair of osteoporotic bone defect in ovariectomized rats. J Pineal Res. 2024;76: e12924.
101. Mahapatra C, Kumar P, Paul MK, Kumar A. Angiogenic stimulation strategies in bone tissue regeneration. Tissue Cell. 2022;79: 101908.
102. Saberi A, Kouhjani M, Mohammadi M, Hosta-Rigau L. Novel scaffold platforms for simultaneous induction osteogenesis and angiogenesis in bone tissue engineering: a cutting-edge approach. J Nanobiotechnology. 2023;21:351.
103. Wang H, Wei P, Zhang Y, Li Y, Yin L. LncRNA TCONS_00023297 regulates the balance of osteogenic and adipogenic differentiation in bone marrow mesenchymal stem cells and the coupling process of osteogenesis and angiogenesis. Front Cell Dev Biol. 2021;9: 697858.
104. Zhang J, Pan J, Jing W. Motivating role of type H vessels in bone regeneration. Cell Prolif. 2020;53: e12874.
105. Peng Y, Wu S, Li Y, Crane JL. Type H blood vessels in bone modeling and remodeling. Theranostics. 2020;10:426–36.
106. Zhou J, Li Y, He J, Liu L, Hu S, Guo M, Liu T, Liu J, Wang J, Guo B, Wang W. ROS Scavenging Graphene-Based Hydrogel Enhances Type H Vessel Formation and Vascularized Bone Regeneration via ZEB1/Notch1 Mediation. Macromol Biosci. 2023;23:e2200502.
107. Huang D, Xu K, Huang X, Lin N, Ye Y, Lin S, Zhang J, Shao J, Chen S, Shi M, Zhou X, Lin P, Xue Y, Yu C, Yu X, Ye Z, Cheng K. Remotely temporal scheduled macrophage phenotypic transition enables optimized immunomodulatory bone regeneration. Small. 2022;18: e2203680.
108. Yang S, Wang N, Ma Y, Guo S, Guo S, Sun H. Immunomodulatory effects and mechanisms of distraction osteogenesis. Int J Oral Sci. 2022;14:4.
109. Amarasekara DS, Kim S, Rho J. Regulation of osteoblast differentiation by cytokine networks. Int J Mol Sci. 2021;22:2851.
110. Miao Q, Yang X, Diao J, Ding H, Wu Y, Ren X, Gao J, Ma M, Yang S. 3D printed strontium-doped calcium phosphate ceramic scaffold enhances early angiogenesis and promotes bone repair through the regulation of macrophage polarization. Mater Today Bio. 2023;23: 100871.

111. Orvalho JM, Fernandes JCH, Moraes Castilho R, Fernandes GVO. The macrophage's role on bone remodeling and osteogenesis: a systematic review. Clin Rev Bone Miner Metab. 2023;21:1–13.
112. Lee J, Byun H, Madhurakkat Perikamana SK, Lee S, Shin H. Current advances in immunomodulatory biomaterials for bone regeneration. Adv Healthc Mater. 2019;8: e1801106.
113. Li X, Wang Y, Zhao C, Tong L, Wang P, Liang J, Jiang Q, Fan Y, Zhang X, Sun Y. A facile immunoregulatory constructional design by proanthocyanidin optimizing directional chitosan microchannel. Small. 2024;2024:e2310689.
114. Wang R, He X, Su S, Bai J, Liu H, Zhou F. Multifunctional tannic acid-based nanocomposite methacrylated silk fibroin hydrogel with the ability to scavenge reactive oxygen species and reduce inflammation for bone regeneration. Int J Biol Macromol. 2024;266: 131357.
115. Ma X, Wang R, Yu S, Lu G, Yu Y, Jiang C. Anti-inflammatory activity of oligomeric proanthocyanidins via inhibition of NF-κB and MAPK in LPS-stimulated MAC-T cells. J Microbiol Biotechnol. 2020;30:1458–66.
116. Hu P, Li K, Peng XX, Kan Y, Yao TJ, Wang ZY, Li Z, Liu HY, Cai D. Curcumin derived from medicinal homologous foods: its main signals in immunoregulation of oxidative stress, inflammation, and apoptosis. Front Immunol. 2023;14:1233652.
117. Zhou T, Yan L, Xie C, Li P, Jiang L, Fang J, Zhao C, Ren F, Wang K, Wang Y, Zhang H, Guo T, Lu X. A mussel-inspired persistent ROS-scavenging, electroactive, and osteoinductive scaffold based on electrochemical-driven in situ nanoassembly. Small. 2019;15: e1805440.
118. Chen D, Liang Z, Su Z, Huang J, Pi Y, Ouyang Y, Luo T, Guo L. Selenium-doped mesoporous bioactive glass regulates macrophage metabolism and polarization by scavenging ROS and promotes bone regeneration In Vivo. ACS Appl Mater Interfaces. 2023;15:34378–96.
119. Huang L, Zhang S, Bian M, Xiang X, Xiao L, Wang J, Lu S, Chen W, Zhang C, Mo G, Jiang L, Li Y, Zhang J. Injectable, anti-collapse, adhesive, plastic and bioactive bone graft substitute promotes bone regeneration by moderating oxidative stress in osteoporotic bone defect. Acta Biomater. 2024;13:475.
120. Sun W, Guo S, Li Y, Li J, Liu C, Chen Y, Wang X, Tan Y, Tian H, Wang C, Du R, Zhong G, Shi S, Ma B, Qu C, Fu J, Jin X, Zhao D, Zhan Y, Ling S, An H, Li Y. Anoctamin 1 controls bone resorption by coupling Cl(-) channel activation with RANKL-RANK signaling transduction. Nat Commun. 2022;13:2899.
121. Marriott I. Apoptosis-associated uncoupling of bone formation and resorption in osteomyelitis. Front Cell Infect Microbiol. 2013;3:101.
122. Xu J, Yue F, Wang J, Chen L, Qi W. High glucose inhibits receptor activator of nuclear factor-κB ligand-induced osteoclast differentiation via downregulation of v-ATPase V0 subunit d2 and dendritic cell-specific transmembrane protein. Mol Med Rep. 2015;11:865–70.
123. Li J, Deng C, Liang W, Kang F, Bai Y, Ma B, Wu C, Dong S. Mn-containing bioceramics inhibit osteoclastogenesis and promote osteoporotic bone regeneration via scavenging ROS. Bioact Mater. 2021;6:3839–50.
124. Ferraris S, Corazzari I, Turci F, Cochis A, Rimondini L, Vernè E. Antioxidant activity of silica-based bioactive glasses. ACS Biomater Sci Eng. 2021;7:2309–16.
125. Chen M, Wang D, Li M, He Y, He T, Chen M, Hu Y, Luo Z, Cai K. Nanocatalytic biofunctional MOF coating on titanium implants promotes osteoporotic bone regeneration through cooperative pro-osteoblastogenesis MSC reprogramming. ACS Nano. 2022;16:15397–412.
126. Huang Y, Du Z, Zheng T, Jing W, Liu H, Liu X, Mao J, Zhang X, Cai Q, Chen D, Yang X. Antibacterial, conductive, and osteocompatible polyorganophosphazene microscaffolds for the repair of infectious calvarial defect. J Biomed Mater Res A. 2021;109:2580–96.
127. Xu K, Mu C, Zhang C, Deng S, Lin S, Zheng L, Chen W, Zhang Q. Antioxidative and antibacterial gallium (III)-phenolic coating for enhanced osseointegration of titanium implants via pro-osteogenesis and inhibiting osteoclastogenesis. Biomaterials. 2023;301: 122268.
128. Zhao Y, Tu MJ, Yu YF, Wang WP, Chen QX, Qiu JX, Yu AX, Yu AM. Combination therapy with bioengineered miR-34a prodrug and doxorubicin synergistically suppresses osteosarcoma growth. Biochem Pharmacol. 2015;98:602–13.
129. Sistanipour E, Meshkini A, Oveisi H. Catechin-conjugated mesoporous hydroxyapatite nanoparticle: A novel nano-antioxidant with enhanced osteogenic property. Colloids Surf B Biointerfaces. 2018;169:329–39.
130. Gupta S, Qayoom I, Gupta P, Gupta A, Singh P, Singh S, Kumar A. Exosome-Functionalized, Drug-Laden Bone Substitute along with an Antioxidant Herbal Membrane for Bone and Periosteum Regeneration in Bone Sarcoma. ACS Appl Mater Interfaces. 2023.
131. Chen W, Zhang H, Zhou Q, Zhou F, Zhang Q, Su J. Smart hydrogels for bone reconstruction via modulating the microenvironment. Research. 2023;6:0089.
132. Lienemann PS, Lutolf MP, Ehrbar M. Biomimetic hydrogels for controlled biomolecule delivery to augment bone regeneration. Adv Drug Deliv Rev. 2012;64:1078–89.
133. Cao H, Duan L, Zhang Y, Cao J, Zhang K. Current hydrogel advances in physicochemical and biological response-driven biomedical application diversity. Signal Transduct Target Ther. 2021;6:426.
134. Chen Y, Wang X, Tao S, Wang Q, Ma PQ, Li ZB, Wu YL, Li DW. Research advances in smart responsive-hydrogel dressings with potential clinical diabetic wound healing properties. Mil Med Res. 2023;10:37.
135. Li J, Li L, Wu T, Shi K, Bei Z, Wang M, Chu B, Xu K, Pan M, Li Y, Hu X, Zhang L, Qu Y, Qian Z. An injectable thermosensitive hydrogel containing resveratrol and dexamethasone-loaded carbonated hydroxyapatite microspheres for the regeneration of osteoporotic bone defects. Small Methods. 2024;8: e2300843.
136. Schwartzman JD, McCall M, Ghattas Y, Pugazhendhi AS, Wei F, Ngo C, Ruiz J, Seal S, Coathup MJ. Multifunctional scaffolds for bone repair following age-related biological decline: promising prospects for smart biomaterial-driven technologies. Biomaterials. 2024;311: 122683.
137. Sun H, Xu J, Wang Y, Shen S, Xu X, Zhang L, Jiang Q. Bone microenvironment regulative hydrogels with ROS scavenging and prolonged oxygen-generating for enhancing bone repair. Bioact Mater. 2023;24:477–96.
138. Liu S, Lu M, Zhang M, Sun X, Luo B, Wu Y. Multifaceted catalytic glucose depletion and reactive oxygen species-scavenging nanoenzyme composite hydrogel for facilitating diabetic bone regeneration. ACS Nano. 2025.

139. Sun Y, Chen LG, Fan XM, Pang JL. Ultrasound responsive smart implantable hydrogels for targeted delivery of drugs: reviewing current practices. Int J Nanomedicine. 2022;17:5001–26.
140. Han X, Shen J, Chen S, Cai Z, Zhu Y, Yi W, Li K, Cai W, Tao B, Cui W, Bai D. Ultrasonic-controlled, "explosive" hydrogels to precisely regulate spatiotemporal osteoimmune disturbance. Biomaterials. 2023;295: 122057.
141. Zhang Z, Wang R, Xue H, Knoedler S, Geng Y, Liao Y, Alfertshofer M, Panayi AC, Ming J, Mi B, Liu G. Phototherapy techniques for the management of musculoskeletal disorders: strategies and recent advances. Biomater Res. 2023;27:123.
142. Yuan Z, Tao B, He Y, Mu C, Liu G, Zhang J, Liao Q, Liu P, Cai K. Remote eradication of biofilm on titanium implant via near-infrared light triggered photothermal/photodynamic therapy strategy. Biomaterials. 2019;223: 119479.
143. Zheng BD, Xiao MT. Polysaccharide-based hydrogel with photothermal effect for accelerating wound healing. Carbohydr Polym. 2023;299: 120228.
144. Ma K, Liao C, Huang L, Liang R, Zhao J, Zheng L, Su W. Electrospun PCL/MoS(2) nanofiber membranes combined with NIR-triggered photothermal therapy to accelerate bone regeneration. Small. 2021;17: e2104747.
145. Ding Y, Liu G, Liu S, Li X, Xu K, Liu P, Cai K. A multifunction hydrogel-coating engineered implant for rescuing biofilm infection and boosting osseointegration by macrophage-related immunomodulation. Adv Healthc Mater. 2023;12: e2300722.
146. Zhu Y, Liu H, Wu P, Chen Y, Deng Z, Cai L, Wu M. Multifunctional injectable hydrogel system as a mild photothermal-assisted therapeutic platform for programmed regulation of inflammation and osteo-microenvironment for enhanced healing of diabetic bone defects in situ. Theranostics. 2024;14:7140–98.

Publisher's Note