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Plant molecules reinforce bone repair: Novel insights into phenol-modified bone tissue engineering scaffolds for the treatment of bone defects

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ABSTRACT

Bone defects have become a major cause of disability and death. To overcome the limitations of natural bone implants, including donor shortages and immune rejection risks, bone tissue engineering (BTE) scaffolds have emerged as a promising therapy for bone defects. Despite possessing good biocompatibility, these metal, ceramic and polymer-based scaffolds are still challenged by the harsh conditions in bone defect sites. ROS accumulation, bacterial infection, excessive inflammation, compromised blood supply deficiency and tumor recurrence negatively impact bone tissue cells (BTCs) and hinder the osteointegration of BTE scaffolds. Phenolic compounds, derived from plants and fruits, have gained growing application in treating inflammatory, infectious and aging-related diseases due to their antioxidant ability conferred by phenolic hydroxyl groups. The prevalent interactions between phenols and functional groups also facilitate their utilization in fabricating scaffolds. Consequently, phenols are increasingly incorporated into BTE scaffolds to boost therapeutic efficacy in bone defect. This review demonstrated the effects of phenols on BTCs and bone defect microenvironment, summarized the intrinsic mechanisms, presented the advances in phenol-modified BTE scaffolds and analyzed their potential risks in practical applications. Overall, phenol-modified BTE scaffolds hold great potential for repairing bone defects, offering novel patterns for BTE scaffold construction and advancing traumatological medicine.

1. Introduction

Due to the increasing complexity of human activities and population aging, bone defects have received more and more attention as the leading factor responsible for diseases, disabilities and deaths [1]. According to existing studies, bone defects can be attributed to the degeneration, trauma, infection and tumors of the skeletal system [1]. In clinical practice, critical-size bone defects are usually defined as one that would not self-heal after surgical stabilization [2]. The specific size of critical bone defects in human has not gained shared consensus, but is typically described as exceeding 2.5 cm in diameter and affecting more than 50 % of bone circumference [2,3]. Moreover, the sizes of critical bone defects are various in different parts of the body, for example, 1–2 cm (diameter) in tibia and 6–15 cm in femur [3]. Since critical-size bone defects can heal spontaneously, bone implants are desperately required in bone reformation. Natural bones (especially autologous bones are reckoned as the gold standard for bone implants because of their excellent biocompatibility, osteoconductivity and osteoinductivity. However, the scarcity of donors and the risk of immune rejection and antigen spreading limit the application of natural bones, and

Abbreviations: ADSC, adipose tissue-derived mesenchymal stem cell; ALP, alkaline phosphatase; ATG, autophagy-related protein; BMP, bone morphogenic protein; BTC, bone tissue cell; BTE, bone tissue engineering; CA, carnosic acid; CHOP, CEBP homologous protein; CREB, cAMP-response element binding protein; CS, chitosan; CUR, curcumin; ECM, extracellular matrix; ER, endoplasmic reticulum; EGCG, epigallocatechin gallate phosphate; FGF, fibroblast growth factor; GSH, glutathione; GA, gallic acid; HA, hydroxyapatite; HIF-1, hypoxia-inducible factor-1; HO-1, heme oxygenase-1; HUVEC, human umbilical vein endothelial cell; MMP, matrix metalloproteinase; MPN, metal-phenolic network; MSC, mesenchymal stem cell; NO, nitric oxide; Nrf-2, nuclear factor erythroid 2-related factor-2; NOS, nitricoxidesynthase; OPG, osteoprotegerin; OS, oxidative stress; PCL, polycaprolactone; PCLA, polymerization of caprolactone and lactide; RANKL, receptor activator of NF-κB ligand; ROS, reactive oxygen species; Runx2, runt-related transcription factor 2; SA, sinapic acid; SBF, stimulated body fluid; SEM, scanning electron microscopy; SIRT1, silent information regulator of transcription 1; TA, tannic acid; TEM, transmission electron microscopy; TGF, transforming growth factor; TNF-α, tumor necrosis factor-alpha; VEGF, vascular endothelial growth factor; UV, ultraviolet; TCP, tricalcium phosphate; PLLA, poly (L-lactic acid).

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meanwhile, propel the emergence of bone tissue engineering (BTE) based on artificial scaffolds [3,4].

Currently, BTE scaffolds can be classified into metallic scaffolds, ceramic scaffolds, polymeric scaffolds and composite scaffolds according to their substrate materials. Metals, represented by titanium, nickel, magnesium and iron, are the most commonly used materials for BTE scaffolds owing to their high strength and low biotoxicity [5], whereas their excessive density and elastic modulus may compromise osteointegration and lead to aseptic inflammation and bone atrophy/fracture due to the stress-shielding effect [6]. In comparison, ceramic scaffolds based on calcium phosphate and hydroxyapatite possess similar porous structures and chemical components to natural bones, ensuring better osteointegration and adequate mechanical behavior, but still lack durability and stability [7]. Recently, natural and synthesized polymers have risen to be a new choice of BTE scaffolds. Apart from excellent biocompatibility, polymers are also prone to be modified by biomolecules to obtain biological functions and provide active sites to guide cell adhesion, proliferation and differentiation [7–9]. However, most polymer scaffolds suffer from low strength, making them poorly competent for musculoskeletal loading.

Moreover, previous studies have revealed that the efficacy of BTE scaffolds can be undermined by the harsh microenvironment in bone defect sites, including reactive oxygen species (ROS) accumulation, inflammation storm, bacterial infection [10], blood supply disruption and tumor recurrence [11]. Various functional molecules have been consequently induced into BTE scaffolds to address these challenges. The modification of cytokines (VEGF [12], BMP [13], FGF [14], etc.) enhanced the stem cell recruitment/differentiation and angiogenesis. Meanwhile, organic drugs (such as plant extracts [15,16] and antibiotics [17]) and inorganic metal ions [18–20] were incorporated into BTE scaffolds to antagonize inflammation and infection. In view of bone defects caused by tumors, multiple tools, including chemotherapeutics, photothermal effect materials and magnetic nanoparticles [21], have been employed to prevent tumor recurrence. Generally speaking, researchers have manufactured bionic bones via assembling functional molecules, BTE scaffolds and bone tissue cells (BTCs) to develop ideal strategies for bone defect repair.

As a large family of natural drugs extracted from plants and marine creatures, phenolic compounds have recently attracted considerable interest due to their compelling biochemical functions. The commonality of phenolic compounds in biochemical effects is mainly determined by the phenolic hydroxyl group, which binds phenols to other molecules through both covalent interactions and non-covalent interactions (such as coordination interactions, hydrogen bonds, electrostatic interactions and cation-π interactions), and endows polyphenols with strong adhesion to various surfaces [22–24]. For instance, dopamine-based hydrogels have been widely introduced into skin patches to agglutinate wounds and accelerate tissue restorage [25]. Meanwhile, metal-phenolic networks (MPNs) have risen as a powerful method of surface coating [26]. In terms of phenolic effects on cells, thanks to the reductivity of hydroxyl group, phenols serve as a popular antioxidant to eliminate ROS. Meanwhile, more phenolic effects on cell metabolism are being discovered with research progress. Recently, benefiting from their ability of anti-inflammation and immunoregulatory, phenols were adopted to facilitate osteogenesis [27] and bone vascularization [28]. Moreover, studies demonstrated that phenols played a positive role in blocking bone tumor proliferation [29–31]. Despite the frequent involvement of phenolic compounds in bone defect repair, there is still in lack of a systematic review. Herein, we summarized the intrinsic mechanisms of phenolic compounds in bone repair and review the advances in phenol-modified BTE scaffolds, expecting to broaden the application of phenolic compounds in orthopaedic materials and provide a reference for BTE scaffold iteration.

2. Phenolic compounds regulate BTCs

Although being long regarded as a mineral scaffold without any cells, bone is actually a highly cellularized tissue with a high internal porosity that allows cell survival and motility [1] (Fig. 1A). Through secreting extracellular matrix (ECM) and regulating the balance of bone resorption/reformation, BTCs, including mesenchymal stem cells (MSCs), monocytes/macrophages, osteoblasts, osteoclasts and osteocytes, can maintain the elasticity and hardness of normal bones, and achieve osteogenesis in bone defect sites [1,3]. Here, we summarized the inherent mechanisms of phenols' action on BTCs in the following (Table 1).

2.1. The structure and classification of phenolic compounds

As a well-known effective component of plant-derived drugs, phenolic compounds can be easily obtained from tea, fruits, vegetables, cereals and marine food [23]. These organic molecules are characterized by the presence of one (monophenols) or more phenolic hydroxyl groups (polyphenols) (Fig. 1B). Currently, polyphenols have attracted more interest than monophenols due to their enhanced performance in antioxidation, disinfection, and other biological effects [22].

Based on the differences of chemical structures, polyphenols are typically divided into flavonoids, phenolic acids, stilbenes, lignans, and others (Fig. 1C). Represented by catechin and epigallocatechin gallate (EGCG), flavonoids are the most abundant natural polyphenols, possessing two phenyl rings and an oxygenated heterocyclic ring as the molecular backbone [15,22]. Phenolic acids, such as gallic acid and caffeic acid, are derived from benzoic and cinnamic acid, while stilbenoids (including viniferin, resveratrol, etc.) are structurally hydroxylated derivatives of stilbenes [23]. As for lignans, they have a chemical structure similar to mammalian estrogens and construct lignin to support cell wells [22].

2.2. The underlying mechanisms of phenols' effects on BTCs

2.2.1. Phenolic compounds mitigate oxidative damage upon BTCs

Oxidative stress (OS), resulting from excessive ROS accumulation and insufficient antioxidant capacity, is known to cause cellular inflammation, senescence and death, and associated with delayed union or disunion of bone defect. Mitochondria, the cellular hub of energy metabolism, plays a central role in regulating intracellular OS. According to available studies, p38/MAPK [32,33] and JNK/ERK [33,34] pathways and relative effectors/regulators (including activating transcription factors (ATFs) [35], runt-related transcription factor 2 (Runx2) [34], caspase9 [36], etc.) were significantly suppressed by OS, resulting in the attenuation of osteoblast differentiation. Therefore, increasing studies have adopted phenols as natural antioxidants to control intracellular OS [37].

Benefiting from the reductivity of phenolic hydroxyl groups in the structure of phenolic compounds, natural and synthesized phenols are widely adopted in the treatment of excessive-oxidation-associated diseases, particularly bone defect [23]. The depletion of peroxide/superoxide by phenolic hydroxyl groups significantly inhibit intracellular OS [23,28]. Notably, due to the enhanced anti-oxidative efficacy of the single molecule, polyphenols are more likely to be chosen in most studies [28].

Heme oxygenase-1 (HO-1) is one of the most common scavengers of intracellular ROS, making it and its transcriptional regulator named nuclear factor erythroid 2-related factor 2 (Nrf-2) targets of many antioxidants, including phenols. Aberrant glycation often results in a wrong conformation of protein, which can subsequently trigger the mitochondrial dysfunction and ROS accumulation. The administration of glabridin (a flavonoid compound) to glycating-damaged MC3T3 cells was found to effectively eliminate ROS via stimulating the HO-1/Nrf-2 pathway [38].

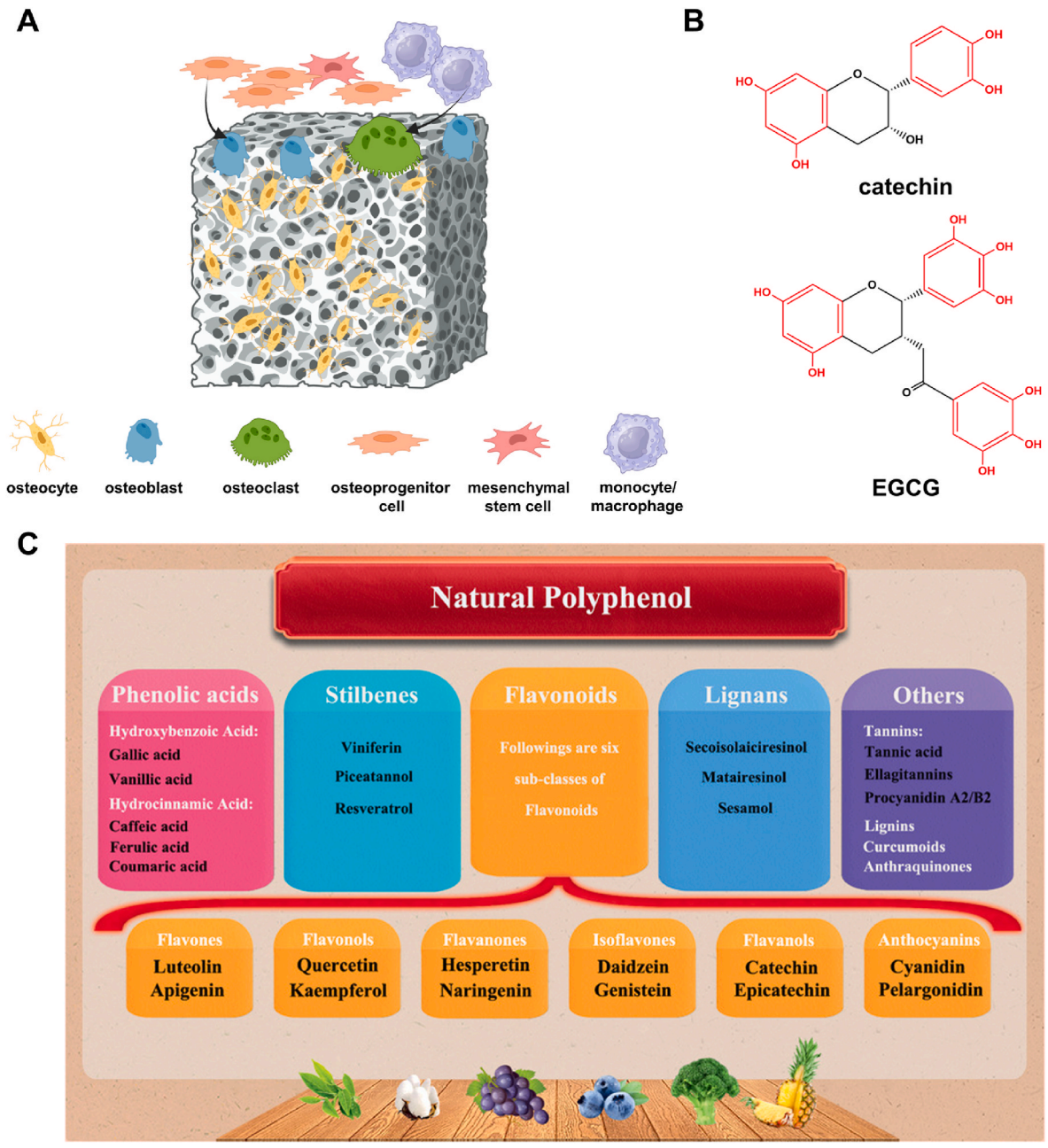

Fig. 1. Phenols regulate BTCs. (A) The profile of bone tissue cells. Osteoprogenitor cells are a special kind of mesenchymal stem cells, which differentiate into osteoblasts and consequently mature to be osteocytes. In the meantime, osteoclasts derive from the fusion and differentiation of precursor monocytes/macrophages. Created with Biorender.com. (B) Phenolic hydroxyl groups (red) in the structure of phenols (represented by catechin and EGCG). (C) The classification of polyphenols. ((C) adapted from Ref. [22].)

Besides, the genesis of nitric oxide (NO), which could facilitate the bioproduction of mitochondrion according to previous studies [39,40], was enhanced by glabridin, indicating phenols' potential effect in restoring the activity of mitochondria. Similarly, carnosic acid (CA) has been reported to stimulate the nuclear translocation of Nrf-2 in osteoclast precursors and upregulate downstream antioxidant enzymes, including HO-1 and NQO-1 [41].

Moreover, the disruption of iron homeostasis also contributes a lot to intracellular OS. Through the Fenton reaction, the iron overloading in BTCs will produce a large amount of ROS and induce lipid peroxidation, leading to impaired mitochondrion, hindered cellular energy metabolism and consequently, ferroptosis [42,43]. Glutathione peroxisome 4 (GPX4) and System-Xc are two core targets impaired in the process from iron overloading to ferroptosis, with the former reducing lipid peroxides and the latter regulating GPX4 production through intracellular transport of glutathione (GSH) [42]. Additionally, it is worth noting that osteoclast differentiation can be promoted by iron overloading through the activation of NF-κB and JNK/ERK pathways [34], which accelerates bone mass loss together with ferroptosis. Recently, curculigoside [44,45] and butein [46] were proved to be modulators of the ferroptosis in BTCs. With the treatment of CUR on iron-overloading MC3T3 cells, the expression and nucleus-translocation of Nrf-2 and FoxO1 (a transcription factor involved in antioxidation and osteogenesis) were enhanced while the IGFR/AKT pathway was suppressed, which synergistically increased GPX4 expression and inhibit ferroptosis [44]. The same pathway of *anti*-ferroptosis was also observed in theaflavin-3,3′-digallate [45].

Overall, the antioxidant mechanism of phenols in BTCs is achieved

Table 1
The effects and relative mechanisms of phenols on BTCs.

Biological Function	Regulating Level	Phenols	Involved Signaling Pathways	Models	References
Anti-oxidation	Molecular biological process	Glabridin	HO-1/Nrf-2 (+), nitric oxide (NO) (+)	MC3T3 cells	[38]
		Carnosic acid	HO-1/NQO1/Nrf-2 (+)	RAW 264.7 cells	[41]
		Curculigoside	Nrf-2/FoxO1 (+), IGFR/AKT (−)	MC3T3-E1 Cells	[44]
Anti-inflammation	Molecular biological process	CUR xanthorrhiza supercritical extract, xanthorrhizol	MAPK/AP-1 (−)	RAW 264.7 cells	[51]
		Extract of Beibu Gulf coral-derived fungus Acremonium sclerotigenum GXIMD 02501	NF-κB (−)	RAW 264.7 cells	[52]
		Sinapic acid, urolithin A	NLRP3 inflammasome (−)	Bone marrow-derived macrophages, RAW 264.7 cells	[58,59]
Pro-autophagy	Molecular biological process	Estradiol, Res	PI3K/Akt/mTOR (−)	MC3T3-E1 cells	[65,66]
		Res	AMPK/JNK (+)	MC3T3-E1 cells	[66]
Anti-autophagy	Molecular biological process	Orcinol glucoside	Nrf2/mTOR (+)	RAW 264.7 cells	[69]
Anti- osteoclastogenesis	BTC behaviors	Carnosic acid, paeonol, EA	Nrf-2/NF-κB (−), MAPK/JNK/ERK/p38 (−)	RAW 264.7 cells	[52, 77–83]
		Methyl gallate, agrimohol	Akt/Btk-PLCγ2 (−), Blimp1 (−), c-Fos/NFATc1 (−)	RAW 264.7 cells	[84,85]
		GA	AKT/ERK/CREB (−)	RAW264.7 cells	[87]
		Dehydrodiconiferyl alcohol	AMPK (+)	RAW264.7 cells	[88]
		CUR	ABCA1/ABCG1/CAV-1 (+)	RAW264.7 cells	[91]
Pro-osteoblastogenesis	BTC behaviors	CUR	BMP2/Smad (+), Wnt/β-catenin (+), endoplasmic reticulum stress (+)	Mesenchymal stem cells	[94]
		Syringic acid	miR-21-5p-mediated Smad7 pathway inhibition	Mesenchymal stem cells	[98]
		Res	miR-193a/SIRT7/NF-κB (−)	Mesenchymal stem cells	[99]

Abbreviation: EA: ellagic acid; GA: gallic acid; CUR: curcumin; (+): activated signaling; (−): inhibited signaling.

by two main pathways, the one is through their intrinsic reducibility, and the other is through enhancing the expression of antioxidant enzymes (such as HO-1 and GPX4) and their regulators to eliminate ROS and alleviate oxidative damage. Thus, phenols are able to inhibit the ROS-mediated apoptosis and ferroptosis in BTCs, and consequently bring a better osteogenesis.

2.2.2. *Phenolic compounds suppress the inflammation of BTCs*

The local inflammation mediated by macrophages in bone defect sites is the crucial cause of BTC injury and BTE failures [47]. Existing studies have revealed that under the regulation of different cytokines, initial macrophages (M0) can polarize into a classically activated form (M1) or an alternative activated form (M2), the former of which releases IL-1β、TNF-α、IL-6 to aggravate the inflammation while the latter reduces inflammation and promotes tissue repair by secreting IL-4, IL-10, and TGF-β [43,47,48]. After phagocytosing the debris of bone implants, macrophages secrete inflammatory factors to promote the M1 polarization, triggering the local aseptic inflammation and bone destruction [49]. Moreover, inflammation also stimulates BTCs to secrete RANKL, which subsequently induces precursor macrophages to differentiate into osteoclasts [50]. Currently, phenols have been widely reckoned as a powerful agent of anti-inflammation. In addition to downregulating inflammatory signaling pathways (such as the MAPK/AP-1 pathway and the NF-κB pathway [51,52]), phenols are also able to restrain the M1 polarization of macrophage via blocking the release of macrophage colony-stimulating factor (*M*-CSF) and pro-inflammatory interleukins [53–55].

Furthermore, inflammasome pathways also make a notable contribution to the cellular inflammation, especially the NLRP3 inflammasome pathway [56]. Stimulated by exogenous substances, the sensory protein NLRP3 recruits and transmits signaling molecules to apoptosis-associated speck-like protein containing a CARD (ASC), which subsequently activates the effector protein caspase-1 to cleave and functionalize the precursors of IL-1β and IL-18, resulting in accelerated inflammation [51,57]. A study in macrophages revealed that IL-1β and caspase-1 were selectively inhibited by sinapic acid (SA), a phenolic acid, in releasing phase triggered by NLRP3 inflammasomes, without impeding the synthesis of pro-IL-1β and IL-6 or silencing the STAT/MAPK/NF-κB signaling pathway, which is closely relative to the regulatory or initial phase of the NLRP3 inflammasome pathway [58]. Another noteworthy fact was that the action of SA on the NLRP3 inflammasome pathway was separated from the AIM2 and NLRC4 inflammasome pathways, highlighting the specificity of SA in the type of inflammasome [58]. Moreover, phenols could regulate the NLRP3 inflammasome through bypass as well. A pomegranate-derived phenol urolithin A (UA) was found to downregulated the NF-κB pathway for the suppression of NLRP3 pathway, suggesting that phenols could block inflammasome pathways in an indirect manner [59].

In addition to macrophages and inflammasomes, many classical pathways are also related to the inflammation in BTCs, for example the MAPK and JNK-STAT signaling pathways. The complexity on the sources of cellular inflammation and properties of phenolic compounds determines that the mechanisms of phenols on inhibiting inflammation are heterogeneous, demanding a deeper inquiry and developing novel phenols for anti-inflammation.

2.2.3. *Phenolic compounds modulate the autophagy of BTCs*

Autophagy is a highly conserved catabolic pathway existing in eukaryotic cells and usually classified into macroautophagy, microautophagy and chaperone-mediated autophagy, depending on the methods of cargo capture. Generally, autophagy can be either adaptive to cope with nutrient and oxygen deprivation or constitutive to eliminate abnormal proteins or organelles [60]. Autophagy-related proteins (ATGs) are the major effectors of autophagy that engage in the recruitment of isolation membranes, the screening and loading of cargo, the formation of autophagosomes and the fusion of autophagosomes and

lysosomes [61]. Their expressions are enhanced with the stimulation of the AMPK signaling pathway, but negatively regulated by the mTOR pathway [61]. In terms of BTCs, recent studies have indicated that the restoration of autophagic flux in osteoblasts significantly reduces the drug-induced oxidative stress and restores mitochondrial homeostasis [62]. These effects not only inhibit osteoblast apoptosis, but also promote osteoblast mineralization and bone mass gain [63]. Similarly, autophagy activation has been shown to contribute to osteoclast survival under stimuli such as ROS and to propel osteoclast differentiation, which has an impact on osteolysis and bone remodeling [64].

The past half decade has witnessed the academic development of phenols' effect on the autophagy of BTCs. Mediated by the ERK pathway, estradiol was found to promote the osteoblast differentiation via inhibiting the phosphorylation of mTOR [65]. Meanwhile, the methods for resveratrol (RSV) to enhance autophagy are more complicated. On the one hand, RSV increase the expression of the silent information regulator of transcription 1 (SIRT1) in osteoblasts to downregulate the activity of the PI3K/Akt/mTOR signaling pathway [66], and on the other hand, the AMPK pathway, a positive regulator of autophagy, was stimulated by RSV in osteoblasts and osteocyte-like cells (MLO-Y4 cells) [67,68]. These two activated pathways synergistically facilitated the osteogenic progress. In terms of the autophagy of osteoclasts, Wan Gong et al. employed a phenolic glycoside named orcinol glucoside (OG) to increase the production of Nrf-2 in osteoclast precursors to phosphorylate the mTOR signaling, resulting in the blockage of ROS-induced autophagy [69]. Another study regarding three phenolic acids (tannic acid (TA), gallic acid (GA) and ellagic acid) also confirmed their negative effects on the autophagy of osteoclasts via decreasing ROS, intracellular Ca^{2+} content and mitochondrial membrane potentials [70].

It seems that phenols usually served as a facilitator of osteoblast autophagy and an inhibitor of osteoclast autophagy. However, the fact could be more intricated. A study of Ke et al. demonstrated that the curcumin (CUR) performed as an autophagy promotor in osteoclasts when it was administered alone, whereas suppressed the autophagy when co-administered with another autophagy promoter RANKL [71]. Further evidences of molecular experiments and transmission electron microscopy (TEM) images revealed that CUR blocked the RANKL-induced formation of autolysosomes and rescued the TRAF3 (an osteoclastogenesis inhibitor) from being degraded by autolysosomes, which synergistically attenuated osteoclast differentiation and bone resorption. Meanwhile, the suppressed osteoclastogenic effect of CUR was found to be boosted by an autolysosome stabilizer chloroquine, supporting the opposite roles CUR played in osteoclast autophagy.

In general, phenols tend to enhance the autophagy in osteoblasts to boost the elimination of harmful cellular components and stimulate osteogenic-associated signaling pathways, facilitating the osteogenic differentiation. However, the autophagy in osteoclasts is usually suppressed by phenols, which triggers the disorder of cell metabolism and results in an inhibited osteoclastic activity. This synergistic effect enhances the process of osteogenesis. However, there is still some negative crosstalk existing at cellular and molecular levels, which pose a potential risk for phenol-modified BTE materials. Therefore, more investigations are in urgent need to figure out more details of phenol's effects on BTC autophagy.

2.3. Phenolic compounds modulate the behaviors of BTCs

2.3.1. Phenolic compounds attenuate osteoclast differentiation

Derived from the monocytic/macrophage lineage, osteoclasts are modulated by osteoblasts and immune cells to alter the local pH and release matrix metalloproteinases (MMPs)/cathepsin K (CTSK), facilitating osteolysis and bone resorption [72]. Nevertheless, osteoclasts are also able to secrete signaling molecules and cytokines to induce the migration and differentiation of osteoblasts, accelerating bone regeneration [73]. Therefore, it is more accurate to definite the osteoclast as a coordinator of bone reconstruction rather than a destroyer [74].

Secreted by osteoblasts or macrophages, the receptor activator of NF-κB ligand (RANKL) serve as the initiator of osteoclast differentiation. After binding to its receptor RANK located on the membrane of osteoblast, RANKL stimulates the tumor necrosis factor (TNF) associated with factor-6 (TRAF-6) and downstream signaling pathways to synergistically activate the nuclear factor of activated T-cell cytoplasmic 1 (NFATc1) and its transcriptional inducer *c*-Fos [75,76], leading to osteoclast differentiation and maturity. Hence, the effects of phenols on RANKL and its downstream pathways have gained considerable interests. Investigations on carnosic acid, paeonol and ellagic acid indicated that phenols blocked classical pathways (Nrf-2/NF-κB and MAPK/JNK/ERK/p38 pathways) to prevent macrophages from differentiating into osteoclasts [52,77–83]. Additionally, the Akt/Btk-PLCγ2 and Blimp1 signals, which played a promotive role in the synthesis of *c*-Fos/NFATc1, were suppressed by methyl gallate and agrimohol without involving classical pathways, suggesting extra suppressive avenues of phenols on osteoclastogenesis [84,85].

An additional strategy for interdicting osteoclastogenesis is to interfere the combination of RANKL and RANK [86]. The AKT/ERK/JNK axis was the downstream signaling pathway of RANK/RANKL [87]. The administration of GA has been confirmed to hinder the RANKL-induced osteoclastogenesis via inhibiting the AKT/ERK/JNK pathway, suggesting that it could be a potential drug for bone regeneration [87]. Moreover, Wonwoo Lee et al. took a similar tactic to reinforce osteogenesis. They adopted dehydrodiconiferyl alcohol (DHCA) to mimic estrogen and stimulate dormant estrogen receptors in ovariectomized mice. With the activation of the AMPK signaling pathway, restored estrogen receptors significantly inhibited intracellular inflammation and osteoclast differentiation [88].

Cholesterol might be another promising target for osteoclasts modulation. As a normal physiological process in macrophages and osteoclasts, cholesterol efflux is necessary to stabilize energy metabolism and maintain cellular homeostasis [89]. However, cholesterol efflux induced by high-density lipoprotein 3 (HDL3) was found to facilitate the apoptosis of osteoclasts, indicating it potential in counterwork osteolysis and bone resorption [90]. Yuwei Liu et al. pointed out that CUR could increase transmembrane transporters of cholesterol, containing ABCA1, ABCG1 and CAV1, to prevent M0 macrophages from becoming osteoclasts [91].

Through inhibiting the generation and maturity of osteoclasts and promoting the apoptosis, phenolic compounds readjust the balance between osteoblast and osteoclast, preventing excessive bone resorption.

2.3.2. Phenolic compounds enhance osteoblast differentiation

Osteoblasts are the major units that establish and maintain the structure and function of the skeletal system. Induced by BMPs and parathyroid hormone, MSCs differentiate into osteoblasts, and the latter promote the synthesis and mineralization of bone matrix by secreting alkaline phosphatase (ALP), collagen, osteopontin, osteonectin and osteocalcin, and interact with osteoclasts to renew bone tissue [92]. With the osteogenic-specific transcription factor Runx2 as a functional hub, the Wnt/β-catenin, ATF4 (CREB2), TGF-β/BMP2/Smad, Hedgehog, and Notch pathways respond to different stimuli and modulate the differentiation, proliferation, and secretion of osteoblast [93].

In terms of phenols' action on osteoblasts, the BMP2/Smad and Wnt/β-catenin signaling pathways are most widely investigated. Mediated by these two pathways, phenols activate Runx2 to enhance osteoblast differentiation [94]. Additionally, some phenols take a nonclassical strategy of decreasing the generation of Runx inhibitors (GLB, HES1, STAT1, TWIST1, HAND2, etc.) to promote osteoblast differentiation [95,96].

Endoplasmic reticulum (ER) stress is an important means of protective cellular response to harmful stimuli, and considered important to mediate phenolic effects on osteoblast differentiation. CUR and its analogues have been found to activate the Smad1/5/9/Runx2 pathway and induce mild ER stress (marked by immunoglobulin binding protein

(BiP), CEBP homologous protein (CHOP), ATF4), which subsequently increase the expression of ATF6 in MSCs, thereby promoting osteocalcin secretion and enhancing both early and late osteogenesis [97].

Notably, recent studies have suggested that miRNAs are also mobilized by phenols to facilitate osteoblast differentiation through post-transcriptional regulations. The Smad7 was reported to block the TGF-β/Smad-mediated Runx2 expression, whereas miR-21–5p, motivated by syringic acid in MSCs could specifically attenuate the transcription of Smad7 to restore Runx2 [98]. Meanwhile, another miRNA miR-193a targeted SIRT7 to relax the suppression of the NF-κB pathway in BMSCs for osteogenesis hindrance [99]. Through restraining miR-193a, resveratrol alleviated intracellular inflammation and boost bone regeneration [99]. Nevertheless, miRNAs can direct phenols to non-osteogenic effects or even anti-osteogenic effects as well. For instance, CUR promoted the expression of miR-126a-3p in adipose tissue-derived mesenchymal stem cells (ADSCs) to target the Wnt co-receptor named low-density lipoprotein receptor-related protein 6 (LRP6), through which CUR blocked the Wnt/β-catenin signaling-mediated osteoblast differentiation [100].

In spite of massive positive influences phenols have on osteoblast differentiation, they could become an obstacle at some conditions. A study regarding the olive leaf extract hydroxytyrosol (HT) suggested that HT reduced ALP, collagen type I alpha 1 (COL1A1) and Runx2 to promote the adipogenesis differentiation of MSCs, instead of osteogenic differentiation [101]. Additionally, quercetin at a high concentration (10 μM) was also proved to inhibit the osteogenic differentiation of MSCs via increasing γ-catenin without β-catenin [102]. These unexpected actions raise some query for the osteogenic efficacy of phenols, and call for open exploration.

2.3.3. Phenolic compounds regulate the cell death of BTCs

Triggered by deleterious factors in bone defect sites, the death of BTCs is the direct reason for the failure of bone repair. The effects of phenols and phenol-modified materials on resisting cell death have aroused great academic interests due to their long-term application in traditional medicine, but the intrinsic mechanisms are still not fully understood. Herein, we summarized phenols' regulation on cell death in different forms.

Apoptosis is an active process of programmed cell death without intense inflammation or membrane rupture. According to current studies, ER stress and mitochondrial dysfunction rank as the two major inducer of apoptosis, and thus, two major targets of anti-apoptotic phenols as well [103,104]. The PKR-like ER kinase (PERK) is one of the promoters of ER stress and an upstream signal for the apoptotic protein CHOP. Through blocking the PERK/CHOP pathway, a flavonoid nobiletin was adopted to suppress ER stress and reduce methotrexate-induced apoptosis [105]. Moreover, phenols relieve mitochondria damage to prevent apoptosis. Through regulating the mitochondrial permeability [106], restoring the electron transport chain (ETC) [107] and inhibiting mitophagy [108], phenols retard the release of caspases and protect cell from degradation.

Different from apoptosis, pyroptosis is another form of programmed cell death that is characterized by inflammatory damage and membrane collapse [109]. Being stimulated by inflammasomes such as NLRP3 and NLRC4, caspase-1/11/4/5 cleave the key effector of pyroptosis gasdermin D (GSDMD) and convert it into an active form to punch the plasma membrane, resulting in a fatal cytoplasm leakage and local inflammation [110]. Since pyroptosis is intimately relative to cell inflammation, anti-inflammatory pathways are deeply involved in the suppression of phenols on pyroptosis. The NLRP3/IL-1β signaling pathway, as the most important terminal regulator of pyroptosis, is also the most common pathway blocked during the administration of phenols, such as quercetin, casticin and icariin [111]. Additionally, the key modulators of intracellular OS, Nrf-2 [112] and HIF-1α [113], are controlled by phenols to lower the intracellular OS level and reduce the OS-induced inflammasomes and caspases.

Through modulating upstream events such as inflammation and OS and downstream effectors such as caspases, phenolic compounds are usually considered positive in decrease the death of BTCs. However, another non-negligible fact is that some harmful phenols, represented by a synthesized phenol named bisphenol A (BPA), can possibly promote apoptosis. Yun Zhang et al. discovered that BPA upregulated the expression of IL-1β and IL-18 via the NLRP3-ASC/caspase1 pathway to induce the pyroptosis of MLO-Y4 cells [114]. Besides, a large amount of ROS accumulated in BPA-treated MLO-Y4 cells, which was speculated to be the upstream stimulators of the NLRP3 signaling pathway because of the reduction of inflammasomes and many downstream proteins resulted from its eradication [114]. Accordingly, it depends on the properties of themselves and their target cells whether phenols function as a pro- or anti-cell death effector.

3. Phenols ameliorate the microenvironment of bone regeneration

Bone defect repair has been confirmed as a systematic engineering that involves the optimization of BTCs and the bone defect microenvironment. Since traumas are usually coupled with deficient blood supply, new vessels are urgently required in bone defect sites to provide oxygen, nutrients and growth factors. Besides, an adequate ingrowth of nerve is also necessary to nourish bones and regulate the differentiation of hematopoietic cells and osteoblasts. In terms of the negative factors against bone regeneration, bacterial infection and the recurrence of residual tumors rank as the two major causes leading to bone repair failures [115]. As shown in Fig. 2, phenolic compounds can make a difference in bone remodeling through modulating these crucial events.

3.1. Phenolic compounds counter against bone infection

Native and contaminated implants-induced infections have been confirmed as serious threats to BTE [116]. Through proactively invasion or secreting toxins, pathogenic bacteria disturb the genetic information and metabolism of osteoblasts, causing osteogenesis hindrance [116,117]. Moreover, the interaction of bacteria and immune cells triggers an excessive production of cytokines (TNF-α, interleukin, RANKL, etc.), leaving inflammatory damage to BTCs and accelerating osteoclast generation [116]. On the other hand, the bacteria-caused exhaustion of neutrophils and M2 macrophages aggravates a deficient bone remodeling [118].

As a common active ingredient of many traditional medicines, phenols have been applied to treat infectious diseases, especially antibiotic-resistant bacterial infections [119]. Due to the variety of molecular structures, the antibacterial mechanism of phenol-based drugs involves different aspects of bacterial metabolism [120].

Through altering the membrane potential, destroying the respiratory chain or crumbling the cell membrane/cytoderm, phenols block the intracellular energy metabolism to exterminate bacteria [121]. Likewise, enzymes required for bacterial replication and transcription are targeted by phenols to control infection [122]. Moreover, interfering bacterial adhesion and colony formation and neutralizing bacterial toxins have been confirmed as potential mechanisms of phenols' bactericidal functions [119,121,123,124]. Based on these powerful effects, researchers extensively employed phenols to modify BTE scaffolds for disinfection. I-Ting Wu et al. respectively incorporated TA, pyrogallol and GA into calcium silicate bone cement (CSC) to form bone implants, all of which significantly inhibited the growth of *Staphylococcus aureus* and *Escherichia coli* in a dose-dependent manner [125]. Apart from direct mixing, phenols are also deposited on the substrate surface to construct antimicrobial coatings. Polycaffeic acid (PCA, a catecholamine) was utilized to self-assembled MPNs with silver on the surface of Ti tablets, which arrested the proliferation of *Escherichia coli*, Staphylococcus Aureus and *Pseudomonas aeruginosa* [126]. Possessing a similar molecular structure to polycaffeic acid, polydopamine (PDA)

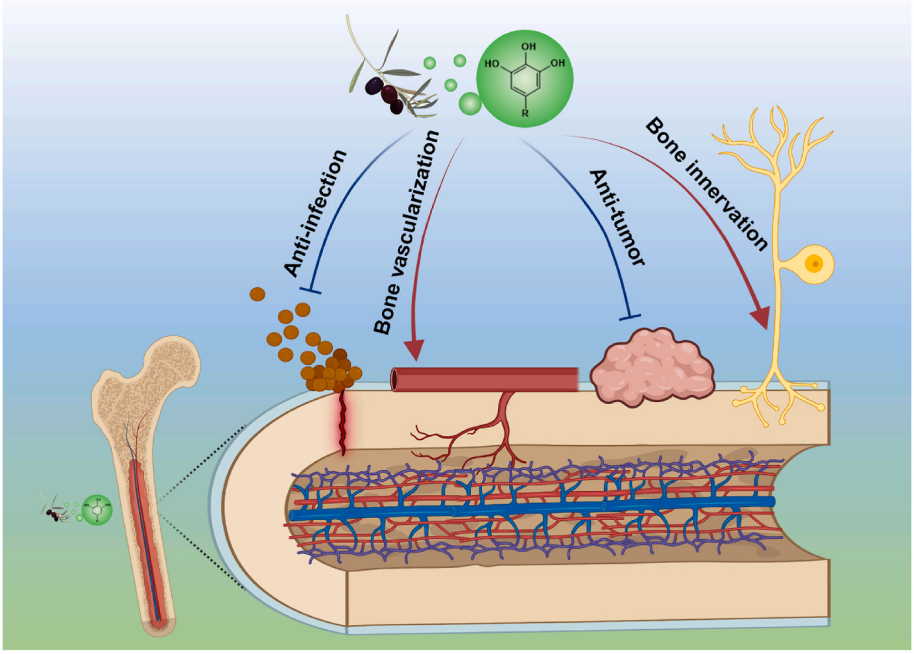

Fig. 2. The schematic diagram for phenols' effects on the microenvironment of bone regeneration. The regulation of phenols on bone environment involves four processes, including anti-infection, promoting the bone vascularization, antagonizing the recurrence of tumor, and potentially inducing the bone innervation. Created with Biorender.com

was also applied in more and more studies to capture metallic ions to exert a synergistic antibacterial effect [127].

3.2. Phenolic compounds facilitate bone vascularization

Since bone is a highly vascularized tissue, it demands a sufficient blood supply to obtain oxygen and nutrients, provide growing signals, and mediate the aggregation of immune cells and stem cells in bone defect sites [128]. However, blood vessels are usually broken or blocked in bone defect sites, which undermines the osteointegration ability of bone implants and results in a delayed union or nonunion [129]. Therefore, it has become an essential goal of BTE to facilitate the angiogenesis in bone defects. Studies have demonstrated that blood vessels are comprised of endothelial cells (ECs) [130,131] and regulated by vascular endothelial growth factor (VEGF) [130], hypoxia and hypoxia-inducible factor-1 (HIF-1) [132], platelet-derived growth factor (PDGF) [133,134] and insulin-like growth factor (IGF) [134]. Meanwhile, nitric oxide (NO)/NO synthase (NOS) [135] and inflammatory factors (IL-1 [136], TNF-α [137], etc.) can modulate the blood flow volume via relaxing or shrinking vessels. Past decades have witnessed the introduction of above factors into BTE scaffolds to adjust bone blood supply.

Several studies indicate that phenols may play a negative role in angiogenesis, whose mechanisms involve inhibiting the expression of VEGF and HIF-1 [138] and reducing MMP9 and MMP13 [139]. Additionally, NO and NOS are also inhibited by quercetin, resulting in an interruption of cell cycle of ECs [140]. On the other hand, cyclooxygenase2 (COX2) is activated by flavones (quercetin and kaempferol) to induce ECM remodeling and vessel deconstruction [141].

Nevertheless, more evidences support that phenols play a positive role in the generation of bone blood vessels. Shi Cheng et al. [142] deposited polydopamine on Ti plates (PDA-1#) and heated PDA-1# in different temperatures to prepare oxidized PDA-2# (150 °C) and PDA-3# (300 °C). Among them, PDA-2# with a middle level of oxidation (9.4 % C═O content) exhibited the most favorable properties for human umbilical vein endothelial cells (HUVECs) to adhere, migrate and form vascular-like structures *in vitro*. This pro-angiogenesis effect of PDA-2# was related to the enhanced expression of VEGF according to the results of biochemical examinations. In addition to the direct effect on HUVECs, more studies have proved that phenols induced stem cells (for example, MSCs) to secrete VEGF, indirectly enhancing the generation of bone blood vessels [143,144,171,172]. Notably, in contrast to the previous conclusion, Qiaoyun Guo et al. found the activity of Nrf-2/HO-1 [143] and eNOS/NO/cGMP pathways [144] were upregulated in phenol-treated HUVECs, while the expression of COX2 decreased, synergistically relaxing vessels and increasing blood supply [145]. Likewise, resveratrol was also shown to boost the bone vascularization through downregulating the local inflammation [188].

In general, phenols play as a positive regulator of bone angiogenesis in most studies, via promoting the generation of pro-angiogenesis factors and inhibit inflammation. However, a few phenols were shown to induce inflammatory factors. Therefore, more investigations need to be conducted to clarify the specific mechanism of phenols' effects on bone vascularization.

3.3. Phenolic compounds antagonize bone tumors

As is known, bone tumors can diminish bone mass and strength through direct erosion and secretion of osteolytic substances, resulting in pathological fracture and bone defect [146]. Furthermore, the recurrence of tumors caused by the inadequate treatment and the drug resistance of tumor cells also decrease the efficacy of BTE scaffolds [147]. Therefore, the development of scaffolds with both tumor-killing ability and bone regeneration potential has been considered as the future trend of BTE applied in bone defect sites with tumors [148,149].

Recently, phenols have achieved remarkable progress in bone tumors treatment. A study regarding *p*-hydroxycinnamic acid (HCA) demonstrated that HCA blocked the G1 and G2/M phases of MDA-MB-231 human breast cancer bone metastatic cells to promote the caspase-3-mediated apoptosis of tumor cells [150]. Additionally, according to the Warburg effect, once the glycolysis pathway gets blocked, tumors will be inhibited due to the deficient energy supply [151]. A flavonoid named apigenin was revealed to inhibit glycolysis-related enzymes GLUT1, HK1 and LDHA in osteosarcoma SOSP-9607 cells, making it

effective in impeding cell generation [152].

Beyond killing tumors, Phenols also attenuate tumor migration/invasion to avoid tumor recurrence. In addition to inhibiting the Wnt/β-catenin signaling for enhanced apoptosis, CUR was reported to downregulate the transcription of miR-21 to stimulate the reversion-inducing cysteine-rich protein with kazal motifs (RECK) protein, significantly hindering the function of tumor invasion-related MMP2 [153]. Furthermore, phenols are able to optimize the tumor microenvironment via eliminating ROS [154]. Ana Lígia Pagnan et al. found that caffeic acid and caffeic acid phenethyl ester functioned of scavenging endogenous ROS, effectively restrained the cell proliferation and angiogenesis in tumors [155]. Moreover, the epithelial-mesenchymal transition (EMT) is a key pre-process that enables tumor cells to migrate and invade. Via restraining the EMT-related pathways, including TGF-β, NF-κB, MAP/ERK, PI3K/AKT and Wnt/β-catenin signaling pathways, a phenol oleuropein blocked the homing and proliferation of tumor cells [156].

3.4. Phenolic compounds manifest potential in retrieving the innervation of bones

It has been confirmed by anatomical and pathological evidences that bones are systematically innervated by autonomic nerves apart from vessels. Sympathetic nerves are generally considered as a negative factor in osteogenesis [157,158]. As the major targets of norepinephrine (NE), α1 and β2 adrenergic receptors are stimulated in the action of sympathetic nerves on bones and subsequently enhance the release of RANKL and osteoclast differentiation [159]. In terms of sensory nerves, substance P (SP) serves as the major mediator between bones and sensory nerves, which contributes to osteogenesis through activating neurokinin receptors and the Runx2 pathway [160,161]. The regulation system of bones in the brain is more complicated than that in the peripheral nervous system. Neuropeptide Y (NPY) functions in the hypothalamus to improve appetite and reduce bone mass through its Y1/Y2 receptors, whereas the leptin shows a paradoxical effect to inhibit bone formation in the central level and promote osteogenesis in the peripheral level [162,163].

Although the particular mechanism of phenols' effects on bone innervation remains unclear, it has been extensively proved that phenolic compounds have the ability to modulate nervous system. Similar to their actions on BTCs, phenols (quercetin, curcumin, catechins, etc.) provide neuroprotection via eliminating ROS, inhibiting inflammation, modulating autophagy and decreasing apoptotic cells, and restore the normal secretory phenotype of neurons [164]. Accordingly, it could be a competitive strategy to use phenols or phenol-modified scaffolds to facilitate the survival and function maintenance of nerves in bone defects, leading to an improved BTE efficacy.

4. The application of phenols in BTE scaffolds

After more than two decades of development, researchers and clinicians have adjusted their requirements for BTE scaffolds from a simple filler to a comprehensive system that simultaneously provides mechanical support, regulate local microenvironment and propel osteogenesis [3]. Due to the low biotoxicity and diverse biological functions, phenolic compounds have been attached great potential to decorating BTE scaffolds [4]. Here, we classified phenol-modified BTE scaffolds into metallic scaffolds, metal-phenolic networks (MPNs), ceramic scaffolds, polymeric scaffolds (containing electrospun, hydrogel and 3D printing scaffolds) and nanoparticle scaffolds, and review their applications on treating bone defects in different models (Table 2).

4.1. Phenol-modified metallic scaffolds and metal-phenolic networks in BTE

Metallic materials represented by titanium are early and widely applied in bone implants because of their excellent mechanical properties, wear resistance, low biotoxicity and low immunogenicity [6]. However, due to a lack of cell-binding sites and bioactive groups, metallic scaffolds are not satisfactory in promoting cell adhesion and modulating tissue microenvironment [6]. Therefore, phenols have been introduced to enrich their biological properties.

4.1.1. Phenol-incorporated metallic BTE scaffolds

In order to construct phenol-modified metallic scaffolds, an immediate approach is to incorporate phenols into metallic substrates through simple mixture or chemical connection. Anna Mieszkowska et al. mixed phloroglucinol (PG) with tropocollagen solution and neutralized the mixture to form a collagen fiber hydrogel (Fig. 3A), which then coated a titanium alloy-based substrate [165]. *In vitro* experiments on osteoblast-like cells (SaOS-2) showed that compared with the control group (Ti and Ti + collagen fibrillar coatings), the addition of PG with high concentration (1.0 mg/mL) significantly enhanced the expression of osteogenesis-associated genes COL1A1, BGLAP and RANKL and reduced inflammatory factors IL-6, TNF-α and MMP2 (Fig. 3B), augmenting the biological functions of the titanium substrate [165]. Meanwhile, phenols also showed remarkable performance in promoting the adhesion between cells and metal scaffolds. The GA-rich extract of Dipterocarpus tuberculatus (MED) was adopted to modify the surface of ozone-treated Ti screws (MED-TIF), which upregulated the intracellular expression of integrin (a molecular marker of cell adhesion) *in vitro* and facilitated the bone regeneration in rat models *in vivo* (Fig. 3C), suggesting MED-TiF could improve the osseointegration in bone defect [166]. Furthermore, there was an interesting fact that the length of incorporating time could alter the effects of phenols on substrates. Sebastian Geiβler found a prolonged time of immersion in phenolic solution (24 h) distinctly hindered the osteogenic effect of the Ti scaffold, while the Ti scaffold with a shorter immersed time (2 h) effectively reversed and accelerated the maturation of osteoblasts [167]. The underlying mechanism still remains to be revealed.

4.1.2. Metal-phenolic networks applied in BTE

Recently, metal-phenolic network (MPN) emerges as a novel method of scaffold surface modification, which broadens the application of phenols. Constructed through the coordination interaction between metal ions and phenols, MPNs are able to spontaneously assemble on the surface to form coatings and customize functions for scaffolds [168]. Due to the presence of phenolic hydroxyl groups, MPNs are naturally adopted to inhibit oxidation. As illustrated in Fig. 4A, Xiujun Tan et al. coupled *C*-alkylpyrogallol arene cages (PgC3) with osteogenic magnesium ions (Mg^{2+}) to form PgC3Mg MPNs, which subsequently eliminated the H_2O_2-induced ROS in BMSCs and accelerated osteogenesis [2]. Moreover, the TA/Mg^{2+} MPN constructed by Min He et al. showed properties of promoting the adhesion and regulating the polarization of macrophages (Fig. 4B) [169]. The analysis of cell phenotype showed that the TA/Mg^{2+} MPN converted the pro-inflammatory/M1 phenotypes (IL-6β, IL-1, TNF-α, CD86 and iNOS) of macrophages into anti-inflammation/M2 phenotypes (IL-4, IL-10, CD163 and CD206), leading to a supportive osteoimmune environment for bone regeneration [169].

As the bacterial infection significantly increases the risk of bone repair failure, the antimicrobial ability has been reckoned as an essential property of MPNs to design and develop. Metal ions such as Ag^{+} and Cu^{2+} have proved to transform the structure of cytoderm, collapse cell membrane, aggravate oxidative stress and block molecular signal transduction to inhibit infection [168,170]. Therefore, polycaffeic acid (PCA) [126] and TA [127] have been grafted to the surface of Ti scaffolds via UV light irradiation and dopamine ligation, respectively, and captured Ag^{+} to form PCA/Ag and TA/Ag coatings (Fig. 4C). Both of the two MPNs demonstrated a significant activity of anti-infection.

In addition to biological functions, the excellent performance in grafting and self-assembly enables MPNs to load and package drugs. Min

Table 2
Phenol-modified BTE scaffolds.

Scaffold Type	Phenol/MPN	Substrate	Biological Function	Mechanical Property	References
Metallic Scaffolds	Phloroglucinol	Ti6Al4V	Pro-osteogenesis Anti-inflammation		[165]
	Dipterocarpus tuberculatus Roxb.	Ti	Enhancing cell adhesion Pro-osteogenesis		[166]
	TA, pyrogallol PG	Ti	Pro-osteogenesis Anti-infection		[167]
Metal-Phenolic Networks	TA/Mg^{2+}	Ti	Pro-osteogenesis Anti-inflammation Immunomodulation		[169]
	Polycaffeic acid/Ag^{+}	Ti	Anti-infection		[126]
	Polydopamine/TA/Ag^{+}	Ti	Anti-infection		[127]
	TA/indomethacin/Fe^{3+}	Ti	Pro-osteogenesis Anti-oxidation immunomodulation		[171]
	TA/Cu^{2+}	PPLA	Drug release control Stem cell recruitment Pro-cell adhesion Pro-osteogenesis		[172]
Ceramic Scaffolds	EA	HA	*Anti*-osteoclastogenesis Pro-osteogenesis		[176]
	Grape pomace extract	HA, TCP	Anti-oxidation Anti-inflammation Pro-osteogenesis		[177]
	1-(5-bromo-2-hydroxy-methoxyphenyl)-ethanone	Sr-dope HA/TiO_2	Pro-osteogenesis		[178]
	TA, pyrogallol	Calcium sulfate plaster	Anti-infection Anti-oxidation	48 ± 8 MPa of compressive strength	[179]
	GA, PG, TA	Calcium silicate-based cement	Anti-infection Anti-oxidation		[125]
Electrospun Scaffolds	CUR	PCL	Pro-osteogenesis		[181]
	Trans-anethole	PCL/PVP	Pro-osteogenesis		[182]
	Pomegranate peel extract	PCL	Pro-osteogenesis		[183]
	Sinapic acid	Chitosan/PCL	Pro-osteogenesis		[184]
	Veratric acid	PCL/PVP	Pro-osteogenesis	0.14 ± 0.01 MPa of tensile strength	[185]
	Lignin	PCL-HA	Pro-osteoconductivity	21.51 ± 0.17–55.56 ± 0.77 MPa of elastic modulus; 8.73 ± 0.21–16.56 ± 0.34 MPa of ultimate tensile strength	[186]
	EGCG	PLLA	Anti-oxidation Pro-osteogenesis		[187]
Hydrogel Scaffolds	Res	PEGDA/TCS	Anti-oxidation Autophagy regulation Anti-apoptosis Pro-angiogenesis Pro-osteogenesis	0.30–0.57 MPa of compressive stress	[188]
	Dopamine	GelMA/HA	Pro-osteogenesis Enhancing stem cell migration Pro-angiogenesis Stem cell recruitment	40~148 kPa of com-pression modulus	[189]
	PG	Hyaluronic acid	Pro-osteogenesis	48~99 kPa of elastic modulus; 2.5–4.9 kPa of compressive modulus	[190]
	TA	Silk fibroin	Anti-oxidation Anti-inflammation Pro-osteogenesis	29.24 kPa of compressive modulus	[191]
	EGCG	Gelatin	Pro-osteogenesis Anti-inflammation		[194,195]
3D-printing Scaffolds	EGCG	PLLA	Pro-osteogenesis *Anti*-osteoclastogenesis Anti-oxidation		[197]
	EGCG	PCL	Pro-osteogenesis Pro-angiogenesis		[198]
	EGCG	PCLA	Anti-infection Pro-osteogenesis		[199]
	TA	Collagen, TCP, Platelet-rich plasma	Drug release control Pro-osteogenesis		[200]
Nanoparticle Scaffolds	TA	Stimulated body fluid	Anti-oxidation Anti-inflammation Pro-osteogenesis		[201]
	Orsellinic acid	Chitosan/gelatin/HA	Pro-osteogenesis		[202]
	Res	PEGylated cyclodextrin	Pro-osteogenesis Anti-inflammation		[206]

Abbreviation: TA: tannic acid; PG: pyrogallol; EA: ellagic acid; GA: gallic acid; CUR: curcumin; EGCG: epigallocatechin gallate; Res: resveratrol; PPLA: poly(L-lactide); HA: hydroxyapatite; TCP: tricalcium phosphate; PCL: poly(caprolactone); PVP: polyvinylpyrrolidone; PLLA: poly-L-lactic acid; PEGDA: poly (ethylene glycol) diacrylate; TCS: thiolated chitosan; GelMA: methacrylic anhydride-modified gelatin; PCLA: polymeriza-tion of caprolactone and lactide.

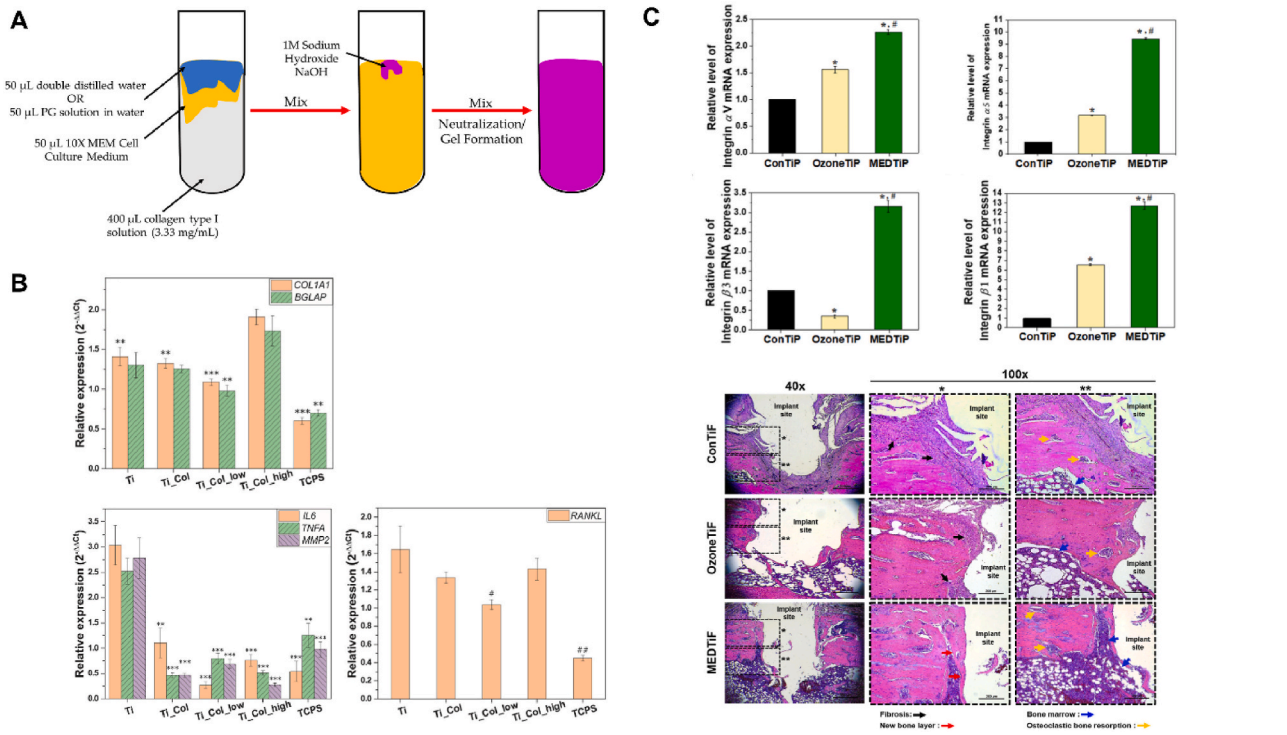

Fig. 3. Phenol-incorporated metal BTE scaffolds. (A) Collagen hydrogels were prepared by mixing PG solution, Cell Culture Medium and collagen type I solution, then neutralizing the solution via dripping NaOH solution to form hydrogels. (B) The PG-modified hydrogel enhanced the expression of osteogenic genes COL1A1, BGLAP and RANKL and inhibited inflammatory factors IL-6, TNFA and MMP2. (C) MED-TiF facilitated the expression of the integrin family in MG63 cells and enhanced osteogenesis *in vivo* estimated by H&E staining. ((A) and (B) adapted from Ref. [165] (C) adapted from Ref. [166].).

He et al. coupled an immunomodulator indometacin (IND) to TA through esterification to form a prodrug TA-IND, then coordinated TA-IND with Fe^{3+} to build an MPN coating for Ti substrates (Fig. 4D) [171]. The coating was stable in ordinary environment but tended to be decomposed by M1 macrophage-secreted esterases to release IND, making it inflammatory-responsive and able to regulate osteoimmune. In another study, the TA/Cu^{2+} coating served as a gated channel for cargos loaded on the PPLA scaffold due to the abundant nanopores derived from the MPN supramolecular structure (Fig. 4E) [172]. As statistics showed, the TA/Cu2+ coating prolonged the releasing duration of standard Rhodamine B from 60 to 500 h, as well as that of BMP2 from 120 to 480 h. The above studies have suggested MPNs a potential regulator for self-adaptive drug release.

4.2. Phenol-modified ceramic scaffolds in BTE

Natural bones possess excellent mechanical properties to support the body and protect internal organs. Studies have figured out that the mechanical properties vary in different parts of bones [3,173]. The yield strength, tensile strength and Young's modulus of human cortical bones are respectively 105–114 MPa, 35–283 MPa and 5–20 GPa, while those of human cancellous bones are determined as 1.0–12 MPa, 1.5–38 MPa and 0.01–1.6 GPa, which endows bones with the outstanding osteoconductivity and osteoinductivity [173]. Bioactive ceramic materials including calcium phosphate-based hydroxyapatite (HA), tricalcium phosphate (TCP) and silicate-based bioactive glass and calcium silicate possess an inorganic composition analogous to natural bones, making them ideal for BTE scaffolds [174]. Additionally, the incorporation of phenols into ceramic scaffolds has deeply expanded their biochemical reactivity.

Being the most emerging ceramic material, hydroxyapatite (HA) has a molecular formula of $Ca_{10}(PO_4)_6(OH)_2$, which is consistent with natural bones in chemical composition [175]. Agung Satria Wardhana et al. found that a direct mixture of ellagic acid and HA powder could accelerate the osteogenesis and reduce the expression of RANKL to suppress osteoclast activity [176]. Another attempt introduced an extract of GA-rich grape pomace into a hybrid scaffold containing HA and TCP. The phenolic extract significantly enhanced the antioxidant capacity of the scaffold and contributed to inhibit the intracellular inflammation of SaOS2 osteoblast-like cells [177]. Furthermore, Qiong Yuan et al. developed a novel relationship of HA and phenols, in which HA served as a mediator between the phenol-loaded substrate and cells. They deposited strontium-doped HA (SrHA) on the surface of TiO_2 nanotubes and used the TiO_2/SrHA scaffold to load 1-(5-bromo-2-hydroxy-methoxyphenyl)-ethanone (BHM), preparing the TiO_2/SrHA/BHM scaffold [178]. As shown in Fig. 5A and B, the SrHA coating served as cell anchors to made TiO_2 nanotubes easier for cell adhesion and steadied the release of BHM with abundant micropores, which indirectly optimized the osteogenic effect of the TiO2/SrHA scaffold [178].

Calcium sulfate-/calcium silicate-based scaffolds are also promising candidates for BTE. Recently, researchers have noticed the important role of phenols in enhancing the anti-infection ability of BTE scaffolds. Naji Kharouf et al. contrasted the antibacterial property of calcium sulfate plaster scaffolds infused with TA or pyrogallol (PY) and found the addition of these two phenols could increase the anti-bacterial effect of the scaffolds 20-fold compared with pristine plaster, resulting in a thorough elimination of *Staphylococcus aureus* (Fig. 5C), a common bacterium in bone infection [179]. Similarly, another study incorporated GA, TA, and PY into calcium silicate-based bone cement, and each of them showed a definite effect of inhibiting *Staphylococcus aureus* and *Escherichia coli.* [125].

Although the introduction of phenols expanded the biological functions of ceramic BTE scaffolds, there was a notifiable fact revealed by Naji Kharouf et al. that the compressive strength of the scaffolds significantly decreased owing to the addition of TA and PY (Fig. 5D) [179], suggesting that more investigation should be conducted to figure out the mechanism of phenols' impact on material strength and more

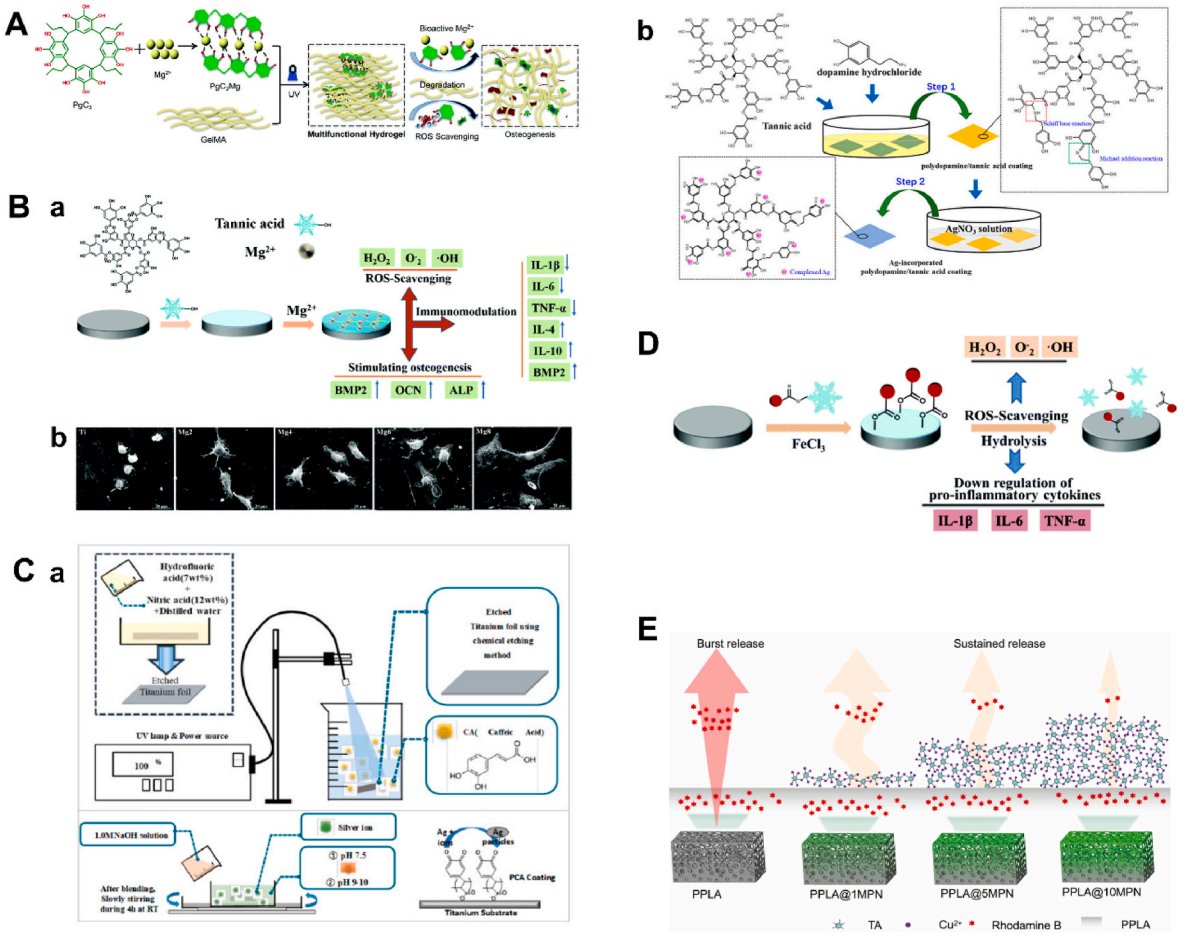

Fig. 4. Metal-phenolic networks for BTE. (A) PgC3 coordinated with Mg2+ to form magnesium-seamed PgC3 cages (PgC3Mg) to scavenge ROS and facilitate osteogenesis. (B) (a) Illustration of the coating process of TA/Mg2+ MPN and its potential biofunctions; (b) Macrophages' morphology after cultured on Ti plates with different coatings for 12 h; scale bar is 20 μm. (C) (a) Schematic illustration of the process of coating polycaffeic acid (PCA) on etched titanium (upper image) and synthesis of metallic silver on the Ti–PCA substrate (lower image); (b) The synthetic procedure and potential reaction mechanism of Ag-incorporated polydopamine/TA coating. (D) Illustration of the coating process of TA–IND/Fe3+ coating and its immunomodulatory mechanism. (E) The TA/Cu2+ coatings inhibited the burst release of Rhodamine B from the PPLA scaffolds in a dose-dependent manner. ((A) adapted from Ref. [2], (B) adapted from Ref. [169], (C) adapted from Refs. [126,127], (D) adapted from Ref. [171] (E) adapted from Ref. [172].).

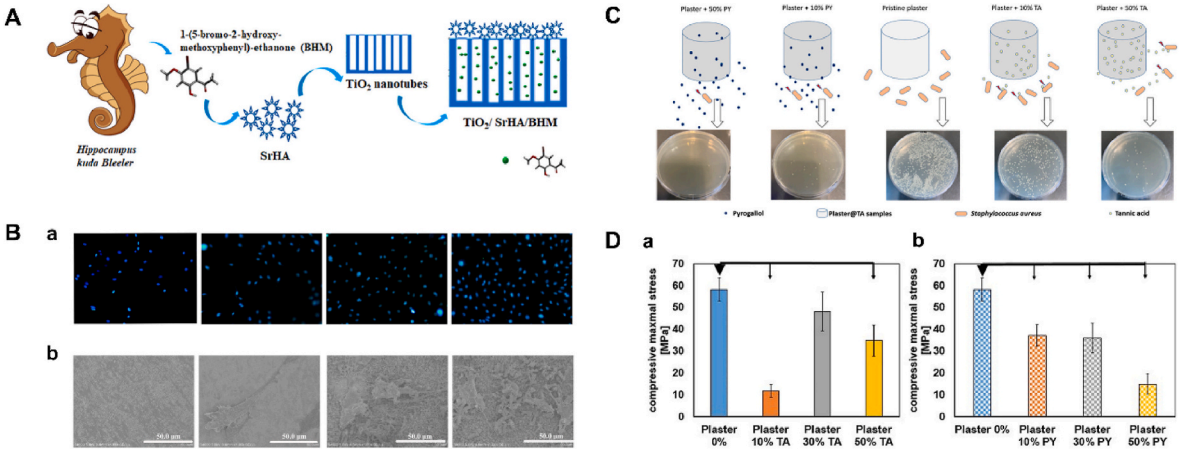

Fig. 5. Phenol-modified ceramic BTE scaffolds. (A) The compound BHM was embedded in the surface-generated SrHA on the TiO2. (B) Fluorescent staining (DAPI) (a) and SEM images (b) of MC3T3-E1 cells adhering to Ti, TiO2, TiO2/SrHA and TiO2/SrHA/BHM (from the left to the right). (C) The addition of PY or TA enhanced the antibacterial effect of plaster compared with pristine plaster in a dose-dependent manner. (D) Evolution of the maximal stress under compression for the pristine plaster, the plaster@TA (a) and the plaster@PY (b) composites ($P < 0.05$ Bold arrows). ((A) and (B) adapted from Ref. [178], (C) and (D) adapted from Ref. [179].).

vigilance should be paid to avoid ceramic BTE scaffolds from disruption.

4.3. Phenol-modified polymeric scaffolds in BTE

As is known, the matrix of bones is rich of biomacromolecular polymers such as type I collagen fibers, which play an essential role in strengthening bones [180]. Meanwhile, the protein- or polysaccharide-based structures of these polymers provide active sites for cell adhesion, and transmit/present biochemical or mechanical signals for cell proliferation and differentiation [180]. Accordingly, natural and artificial polymer scaffolds have been developed to simulate natural bone matrix. Benefited from their diverse composition and properties, polymer scaffolds cover a wide range from soft hydrogels to tough scaffolds for mechanical loadings [180,190]. Here we summarized the application of phenol-modified polymer scaffolds for BTE in different forms, including electrospun fiber, hydrogel, 3D bioprinting scaffold and nanoparticle scaffold. It is noteworthy that in order to improve the mechanical property of polymer scaffolds for mechanical support, polymers are usually incorporated with metallic or ceramic materials to build composite system rather than simple scaffolds, which were also included in the following summary.

4.3.1. Phenol-modified electrospun scaffolds in BTE

Electrospinning refers to the process of endowing the polymer solution with charges and spraying it under a high-voltage electric field to obtain nano-scale fibers [179]. Due to its outstanding simulation of the interlaced collagen fiber network in bone matrix, electrospun scaffolds possess a high porosity and specific surface area that are essential for osteointegration [180]. Recently, phenols have been introduced into electrospun scaffolds to regulate physical and biochemical properties.

A direct mixture of phenols and polymer solution was most widely utilized to produce electrospun BTE scaffolds. CUR [181], *trans*-anethole [182], pomegranate peel extract [183] have been incorporated into PCL-based BTE electrospun fibers through this way (Fig. 6A). Thanks to the *in vivo* stability of polymer fibers, the release period of CUR and *trans*-anethole prolonged to 12 [181] and 25 days [182] respectively. The expression of osteogenic-associated genes ALP, Runx2 and BMP2 was stimulated by the two phenols, resulting in a strengthened osteogenesis and mineralization (Fig. 6B). Moreover, Khadiga M. Sadek et al. noted that the phenol pomegranate peel extract increased the proportion of macropores in the fiber scaffold but decreased that of micropores, resulting in an elevated total porosity and improved cell migration. However, further experiments demonstrated that higher porosity also related to an accelerated degradation of the nanofibers, indicating researchers to balance the scaffold stability and the property of osteointegration [183]. In addition to simple polymer fibers, researchers have developed hybrid electrospun fibers as the substrate to load/encapsulate phenols and smooth their interaction with BTCs. Through the method of ionic gelation technique, sinapic acid [184] and veratric acid [185] were encapsulated by chitosan microspheres and embedded into PCL electrospun fibers, building up a hybrid scaffold (Fig. 6C). Due to the hydrophilicity of chitosan, the composite fibers showed an optimized performance in swelling and protein adsorption compared to simple fibers, which cooperated with phenols to accelerate bone formation (Fig. 6D).

As is universally acknowledged, an adequate mineral deposition is necessary for BTE scaffolds to simulate natural bones. Ding Wang et al. developed a phenol-mediated method of automatic mineralization on

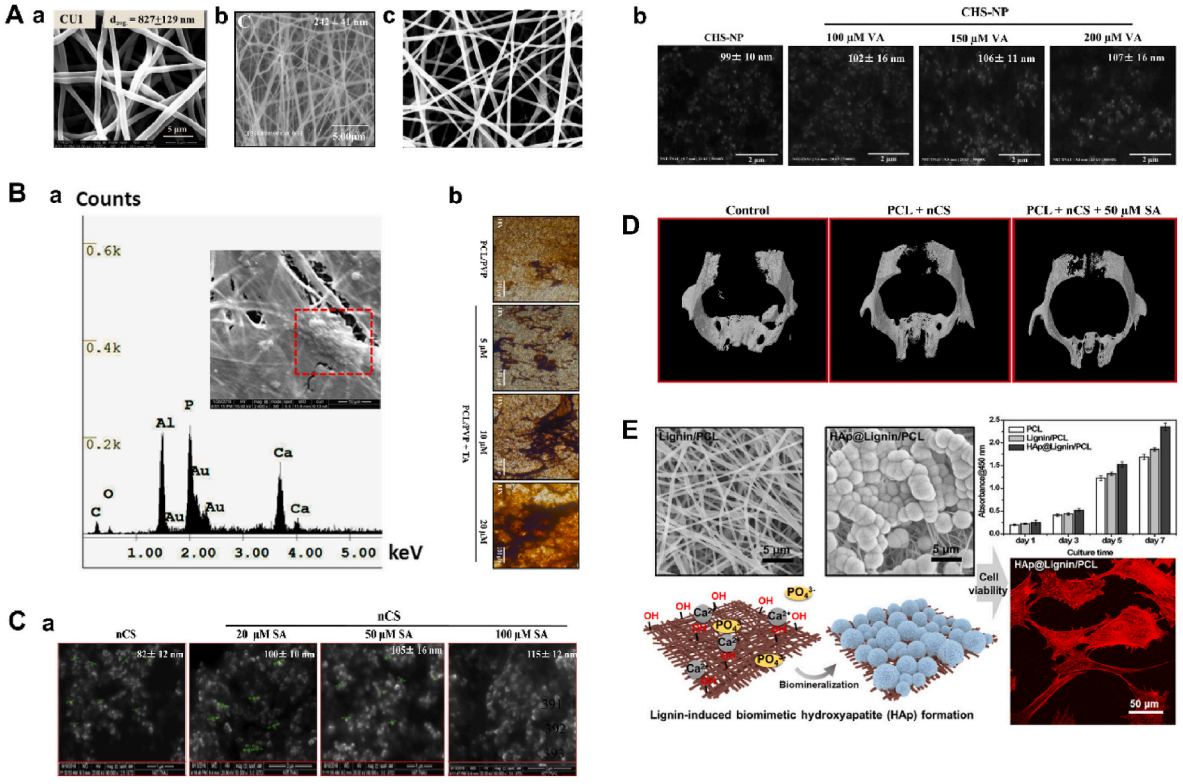

Fig. 6. Phenol-modified electrospun fiber scaffolds in BTE. (A) SEM images of PCL-based electrospun fiber scaffolds doped by CUR (a), *trans*-anethole (b) or pomegranate peel extract (c). (B) (a) The SEM image and EDS spectrum of the Ca and P deposited on the CUR-loaded nanofiber scaffolds; (b) The von Kossa staining of Ca on the *trans*-anethole-incorporated fiber scaffold. (C) SEM images of chitosan microspheres containing sinapic acid (SA) (a) and vanderatric acid (VA) (b). (D) Micro-CT images of calvarial bone defects in rats treated with the chitosan-loading PCL scaffold and the SA/chitosan-loading PCL scaffold for 4 weeks. (E) Lignin/PCL fibrous platform was prepared by electrospinning, followed by incubation in a SBF. Lignin donated abundant hydroxyl groups to bind with metal ions and facilitate the nucleation and growth of HA, leading to enhanced osteogenesis. ((A) adapted from Refs. [181–183], (B) adapted from Refs. [181,182], (C) adapted from Refs. [184,185], (D) adapted from Ref. [184] (E) adapted from Ref. [186].).

electrospun fibers [186]. They prepared a lignin-doped electrospun PCL nanofiber film (lignin/PCL) and employed the hydroxyl groups of lignin to capture Ca and P in simulated body fluid (SBF) (Fig. 6E). SEM images showed that hydroxyapatite nucleate on the film after 2-day incubation and extended into a uniform coating (lignin/PCL/HA) in another 5 days (Fig. 6E). According to mechanical analysis, the elastic modulus of the film increased from 10.23 ± 0.65 MPa (simple PCL fiber) to 55.56 ± 0.77 MPa (lignin/PCL/HA fiber) and even 5.57 ± 0.73 GPa (the HA layer on the surface of fiber), which was conducive for osteoinductivity [186]. Meanwhile, another study regarding EGCG-coated mineralized PLLA fibers also confirmed the combination of phenol (EGCG) and minerals could amplify their pro-osteogenic effects [187], which was attributed to the ROS-eliminating ability of EGCG and the supplement of bone matrix from minerals, emphasizing the importance of phenol-modified hybrid electrospun scaffolds in BTE.

4.3.2. *Phenol-modified hydrogel scaffolds in BTE*

Currently, hydrogel scaffolds for BTE are commonly constituted by biomacromolecules (gelatin, sodium alginate, hyaluronic acid, etc.) and biomacromolecule-derived substances, which allows them to easily interact with cells or be modified through functional groups containing amino, carboxyl and sulfhydryl [191].

In the perspective of biological effects, multiple studies have demonstrated that the combination of hydrogel and phenols diversified the properties of BTE scaffolds including ROS elimination, autophagy recover and osteogenic differentiation [188–191]. Meanwhile, it was observed by Dehui Fan et al. that phenols could serve as a stabilizer in the generation of bone blood vessels [188]. Angiogenin-2 was a key inducer for the early-stage endothelial micro-vascular formation. However, it triggered the local inflammation by increasing the vascular permeability as well, which resulted in the HUVEC apoptosis [188]. Resveratrol was found to stable a sustainable angiogenesis in bones through downregulating the ANG2-induced inflammation [188]. Moreover, as biomechanical investigations have pointed out, rigid matrix can guide MSCs differentiating into osteoblasts more effectively than soft matrix, for which traditional hydrogels with low strength are limited in BTE [192,193]. Fortunately, phenolic modification can make a difference in this problem.

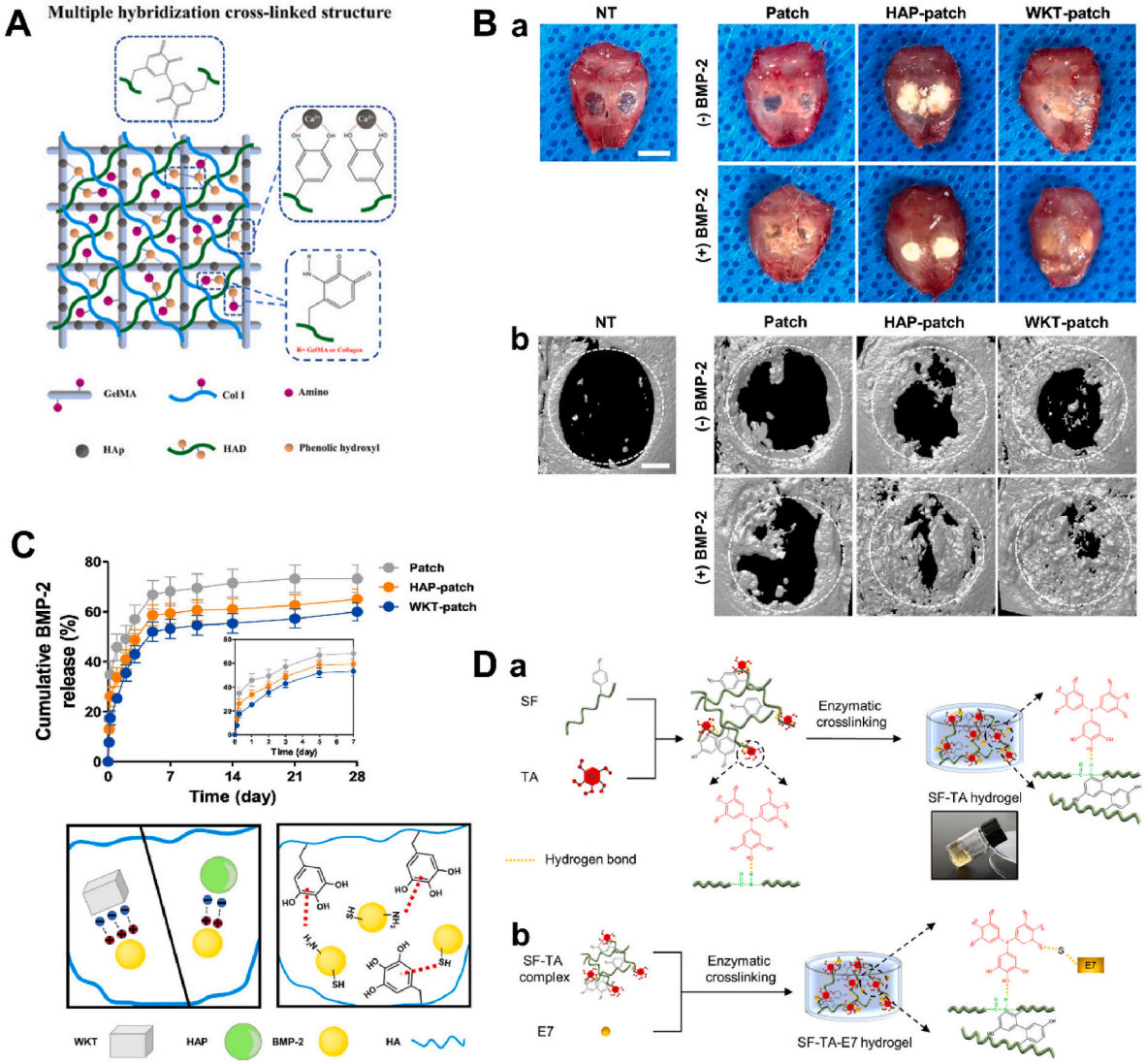

Fig. 7. Phenol-modified hydrogel scaffolds in BTE. (A) Dopamine-modified hyaluronic acid bound to GelMA/HA scaffold via the covalent bond between phenolic hydroxyl groups and amino acids. (B) Gross images (a) and Micro-CT images (b) of mouse calvarial bone defects treated with different patches. Scale bar in (a) = 5 mm. Scale bar in (b) = 1 mm. (C) PG reduced the release of BMP2 contained in hydrogel patches through hydrogen bonds. (D) (a) TA was mixed with SF to build SF-TA hydrogel through hydrogen bonds; (b) E7 peptide was doped into SF-TA hydrogel and formed hydrogen bonds with TA. ((A) adapted from Ref. [189], (B) and (C) adapted from Ref. [190] (D) adapted from Ref. [191].).

Serving as modifying molecules, phenols provide abundant reactive sites, especially active hydroxyl groups, for principal molecules of hydrogel. For instance, dopamine-modified hyaluronic acid formed a covalent connection between the amino groups of GelMA/HA scaffold and phenolic hydroxyl groups (Fig. 7A), bringing the scaffold a twofold increase in elastic modulus and preventing excessive degradation [189]. Similar phenomenon was observed in the combination of pyrogallol (PG) and mineralized hyaluronic acid hydrogel, in which the Ca^{2+} and Mg^{2+} absorbed by PG promoted the repair of rat cranial bones together with the strengthened hydrogel (Fig. 7B) [190]. Additionally, it was noteworthy that the BMP2 loaded in the hybrid hydrogel could be restricted from release due to the electrostatic interaction between its amino groups and PG (Fig. 7C), suggesting that phenols were potential in regulating drug release [190]. Moreover, studies regarding EGCG-modified gelatin sponges demonstrated that the addition of EGCG remarkably reduced the production of MMPs, remodeling the bone matrix into an osteogenic phenotype [194,195].

Furthermore, there is another interesting strategy that phenols are employed as a principal molecule to construct hydrogel. As shown in the study of Wei Zhang et al. they employed TA as a block to crosslink with silk fibroin for gelation and avoided a burst release of BMSC-specific affinity peptide E7 loaded in the gel, both via hydrogen bond (Fig. 7D). Afterwards, with the hydrogel disintegrating, TA blocks diffused to eliminate ROS and cooperate with E7 to facilitate BMSC migration and osteogenic differentiation [191].

In short, phenols not only attach more biological functions to hydrogel scaffolds, but also regulate their biomechanical properties to meet the requirement of BTE.

4.3.3. Phenol-modified 3D bioprinting scaffolds in BTE

Thanks to the progress of additive manufacturing technique and bioink materials, 3D bioprinting has been developed to construct biomimetic scaffolds with complex structures via altering the bioink and printing procedures in different stages [196]. Phenolic compounds are usually designed as coatings to mediate cell behaviors on the surface of 3D printing BTE scaffolds.

Phenols can easily self-assemble into surface coatings in alkaline solution through oxidative polymerization. As illustrated in Fig. 8A, EGCG molecules were proved to polymerize with each other on poly (L-lactic acid) (PLLA) scaffolds and PCL scaffolds in Bis-Tris/NaCl solution and $NaHCO_3$ solution respectively to downregulate oxidative stress and redirect the ADSC differentiation from adipogenesis to osteogenesis [197,198]. In addition to simple coatings, phenols are able to form composite coatings with minerals, simulating the structure of periosteum on BTE scaffolds. With the assistance of silane coupling agent KH550, Xiangchun Zhang et al. linked EGCG to HA molecules and synthesized an artificial periosteum (KH-HA-EGCG) via the self-assembly of EGCG on the surface of polymerization of caprolactone and lactide (PCLA) scaffolds (Fig. 8B) [199]. The complicated KH-HA-EGCG film demonstrated an improved performance in HA deposition and disinfection (Fig. 8C) [199]. Moreover, the result of the live cell ratio test suggested that the modification of phenolic film significantly enhanced the cell proliferation on the PCLA scaffold [199]. Notably, since most phenols are hydrophobic while HA and TCP are hydrophilic, it is difficult to load phenols upon ceramic-rich 3D scaffolds. However, Jianxu Wei et al. proposed a strategy recently to solve this problem [174]. They employed gelatin microspheres, which are hydrophilic, to encapsulate CUR and successfully incorporated it into a 3D scaffold composed of HA, TCP and PCL [174]. The mixed 3D scaffold

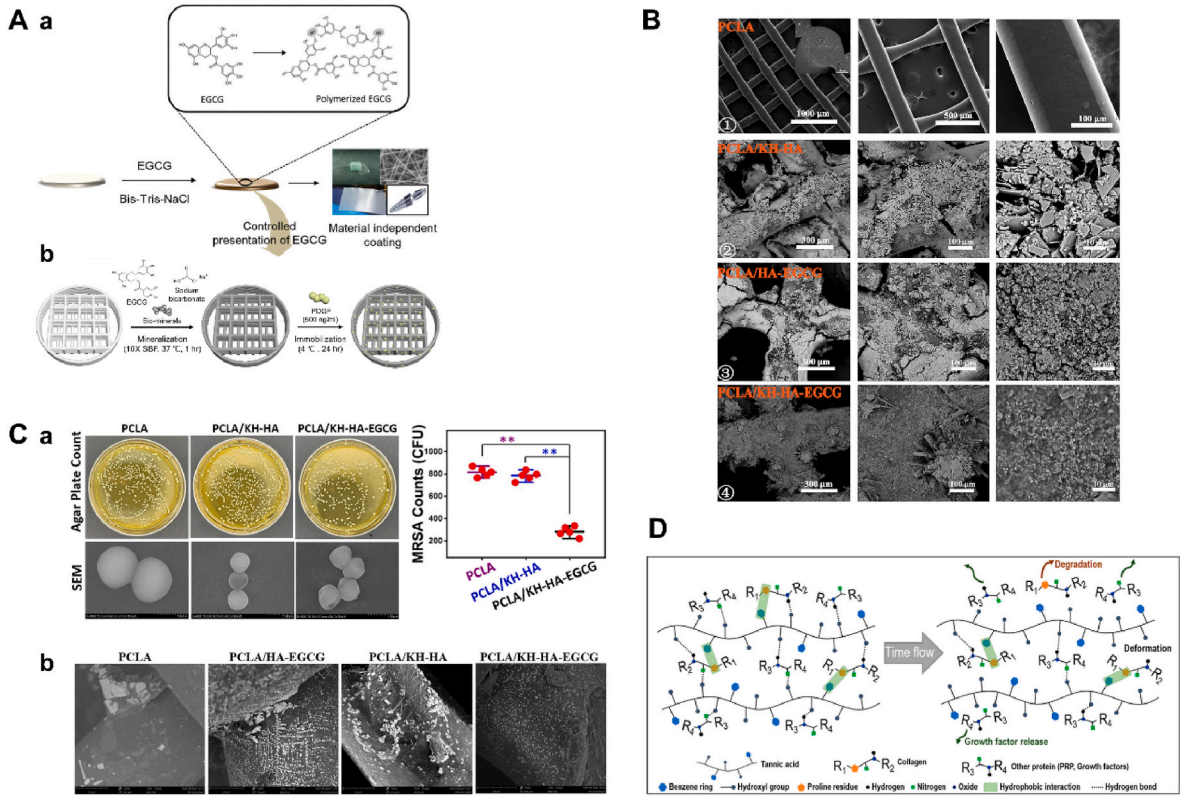

Fig. 8. Phenol-modified 3D bioprinting scaffolds in BTE. (A) Illustrations of manufacturing EGCG-coated PLLA (a) and PCL (b) scaffolds. (B) Representative SEM images showing the structure of pure PCLA, PCLA/KH-HA, PCLA/HA-EGCG and PCLA/KH-HA-EGCG scaffolds. (C) The agar plate counts (a) and SEM images (b) demonstrated that the KH-HA-EGCG coating boost the process of disinfection and mineral deposition of PLCA scaffold, respectively. (D) Schematics of the interactions between TA and collagen/proteins during gelation and degradation. ((A) adapted from Refs. [197,198], (B) and (C) adapted from Ref. [199] (D) adapted from Ref. [200].).

significantly promoted the bone regeneration both *in vitro* and *in vivo* [174].

It is noteworthy that the advancements in low-temperature/room-temperature 3D printing have propelled fragile biomacromolecule materials, such as collagen fibers and growth factors, to become bioink to fabricate 3D scaffolds that accurately mimic human tissue structures. On account of the extensive interactions between phenolic hydroxyl and biomacromolecules, the application of phenols in 3D printing scaffolds has been further broadened. Taking the study by JiUn Lee et al. as an example, they manufactured a 3D printing scaffold constituted by ceramic substrate and tissues, including collagen fibers and plate-rich plasma (PRP), in both low temperature (−16 to −18 °C) and room temperature (38–40 °C) [200]. Meanwhile, TA was incorporated to constrain PDGF and TGF-β1in PRP from a premature loss through the connection of hydrogen bond (Fig. 8D). As a result, the release period of PDGF and TGF-β was prolonged in the phenol-treated group to 35 days, leading to an increased rate of cell proliferation and an activated osteoblast differentiation after a 9-day culture [200].

4.4. Phenol-modified nanoparticle scaffolds in BTE

Benefiting from their high ratio of specific surface area, varied approaches for cargo loading (drugs and cells) and refined delivery and tissue distribution, nanoparticles emerge as a new choice for BTE scaffolds. Therefore, we purposefully discussed phenolic nanoparticle BTE scaffolds here, separately from traditional bulk scaffolds.

With the supramolecular self-assembly in ion-rich solution through the coordination between phenolic hydroxyls and cations, phenols are competitive in forming nanoparticle BTE scaffolds [201]. As demonstrated by the work of Hayeon Byun et al. TA and cations in SBF (Na^+, Ca^{2+} and Mg^{2+}) crosslinked with each other and dispersed into mTN particles with a diameter of 250–350 nm under a centrifugal force (Fig. 9A) [201]. These nanoparticles exhibited the effects of anti-oxidation, anti-inflammation and pro-osteogenesis. Interestingly, the biocompatibility examination indicated that free TA solution in 50 μg/mL could significantly decrease cell viability, whereas mTNs in the same concentration showed no obivious cytotoxicity (Fig. 9B), which could be attributed to the gradual release and dispersion of TA in mTNs [201]. This suggested that nanoparticle scaffolds could be a feasible strategy to simultaneously ensure delivery efficacy and reduce drug toxicity.

Since the non-covalent interactions between phenols and biomacromolecules are prevalent, they can also construct nanoparticles through the host-guest interaction. As shown in Fig. 9C, orsellinic acid (OA) was packaged in chitosan nanoparticles (nCS, with diameters ranging from 115 ± 19 nm to 120 ± 10 nm) through the host-guest

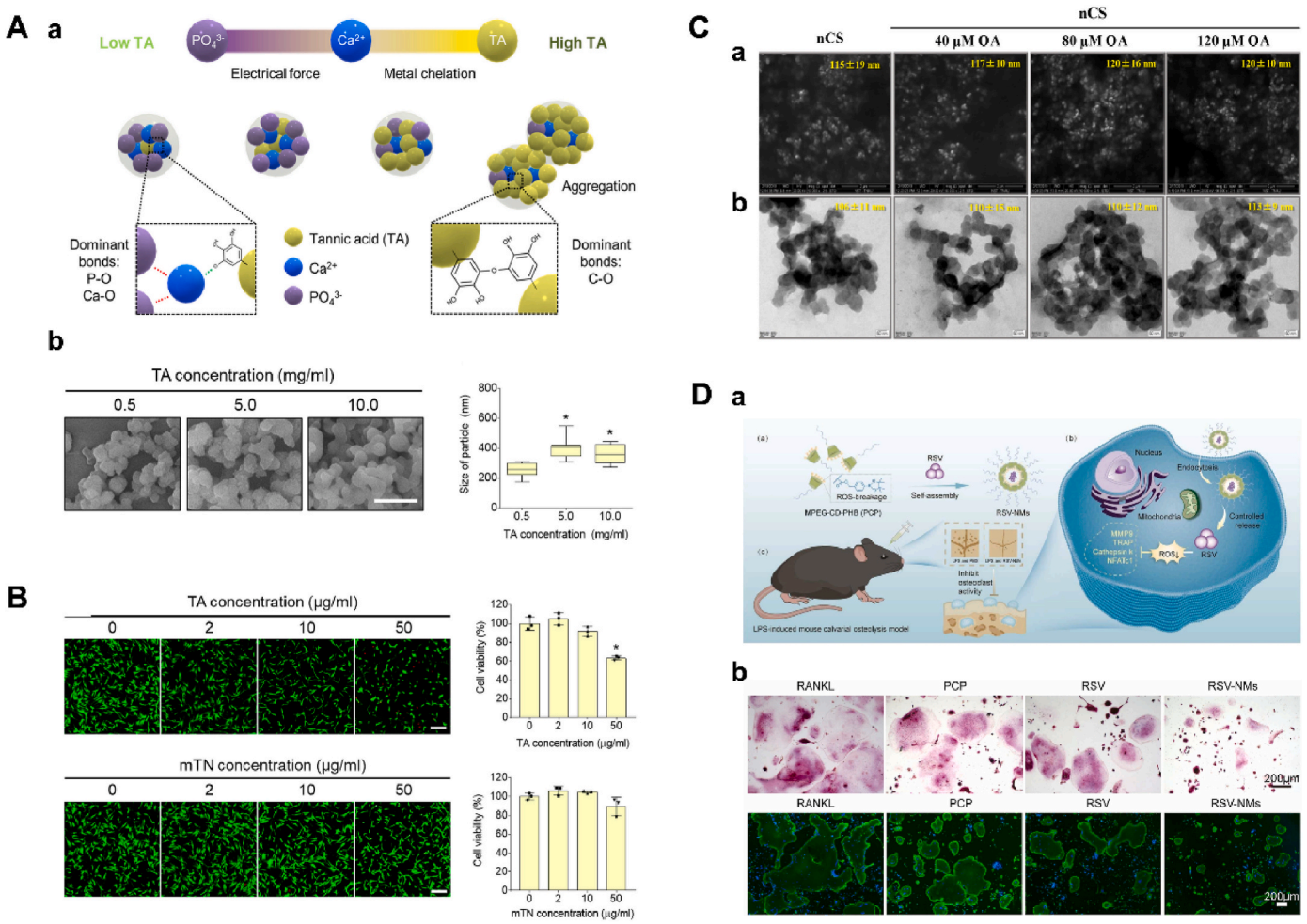

Fig. 9. Phenol-modified nanoparticle scaffolds in BTE. (A) The illustration of mTN fabrication (a) and SEM images of mTNs (b). (B) Live/dead staining and MTT assay results of hADSCs cultured using different concentrations of TA and mTNs (scale bar = 200 μm). *Significantly different compared to the group with no nanoparticles ($p < 0.05$). (C) SEM (a) and TEM (b) images of chitosan nanoparticles (nCS), nCS + 40 μM orsellinic acid (OA), nCS + 80 μM OA, and nCS + 120 μM OA. (D) (a) The synthesis of the ROS-responsive resveratrol-loaded cyclodextrin nanomicelles (RSV-NMs); (b) TRAP staining images in top row and immunofluorescence images in bottom row identified the inhibiting effect of RSV-NMs on osteoclasts. ((A) and (B) adapted from Ref. [201], (C) adapted from Ref. [202] (D) adapted from Ref. [206].).

interaction to improve its poor water solubility and increase the rate of drug utilization *in vivo* [202]. Previous studies have confirmed that the FAK/ERK signaling pathway regulates cell adhesion mediated by integrin, and the osteogenic-related Runx2 is a downstream gene modulated by FAK/ERK [203–205]. Functional assays of OA-loaded nCS revealed that OA activated the FAK/ERK signaling pathway by inducing the expression of integrin α2α5β1, leading to an upregulated expression of Runx2 and other osteogenic-related proteins and accelerating the osteogenic differentiation of MSCs [202].

A more advanced strategy for nanoparticle design is to establish a stimuli-responsive structure for the release of phenols. As illustrated in Fig. 9D, Xiaolin Fang et al. fabricated resveratrol (Res)-loaded cyclodextrin (CD) nanomicelles (Res-NMs) by functionalizing PEG-modified CD with phenylboronic acid ester and subsequently using it to envelop Res, thus obtaining nano-microspheres (in 56.05 ± 5.78 nm of diameter) with an antioxidant core [206]. Additionally, Res-NMs increased the retention of Res in normal environment, but deconstructed with the cleavage of boronic ester bond due to the elevated ROS level. This process ensured an adequate release of Res and attenuate the osteoclast differentiation of RAW 264.7 cells under oxidative stress (Fig. 9D), contributing to the bone defect repair and was supported by the results of *in vivo* experiments [206].

In summary, phenols can easily self-assemble into nanoparticles via the coordination between phenolic hydroxyl groups and cations. The rapid diffusion of nanoparticles endows the loaded drugs with an average distribution, while the combination of phenols and scaffolds extends their metabolic period. Additionally, nanoparticles tend to be phagocytosed by BTCs, thus are able to exert more intracellular functions than traditional scaffolds, fundamentally improving the pro-osteogenic efficacy of phenol-modified scaffolds. Therefore, phenol-modified nanoparticles are expected to become a star material for bone defect treatment in the future.

5. Conclusions and perspectives

With the increasing understanding of bone pathophysiology and advancement in tissue engineering, BTE scaffolds have become the primary means of bone defect repair. Currently, it has been widely acknowledged that an ideal BTE scaffold should possess following properties: biocompatibility, adequate mechanical strength that fits bones, and the ability of pro-angiogenesis and bone microenvironment regulation. As a class of multi-functional drugs derived from plants and fruits, phenolic compounds have been widely employed to prevent and treat inflammation- and senescence-related diseases, as well as construct tissue engineering scaffolds. Here, our review elucidated phenols' roles in bone repair and corresponding mechanisms, demonstrated the profile of phenol-modified BTE scaffolds and finally, presented a perspective for phenol-modified BTE scaffolds.

Accumulated evidences at subcellular and molecular levels have proved that phenols play a positive role in reducing oxidation, alleviating inflammation and modulating autophagy, both through the ROS-eliminating ability of phenolic hydroxyl and regulating intracellular signaling pathways. With the comprehensive influence of these cytological events, phenols boost the MSC differentiation into osteoblast and inhibit the excessive activity of osteoclast, and finally lead to bone remodeling. Meanwhile, phenols also make a difference in bone defect microenvironment. Through eradicating bacterial infection and facilitating angiogenesis, as well as preventing tumor recurrence, phenols provide a mild and nutrient-rich condition for bone regeneration. Considering these powerful effects, phenols have been adopted by BTE scaffolds and cooperate with metal, ceramic and polymer substrates to alter scaffold properties and enhance osteogenesis. The introduction of phenols enforces metal and ceramic scaffolds with strengthened bioactivity. Specifically, phenols endow them with diverse functions containing anti-inflammation and anti-infection, and allow them with improved cell adhesion and cell-material crosstalk. In terms of phenol-modified polymer scaffolds, in addition to osteogenic regulation on BTCs and infection clearance, phenols are also employed to alter the porosity of these scaffolds and promote scaffold mineralization via capturing metallic ions, to obtain a better osteoinductivity and osteoconductivity of BTE scaffolds. Especially, phenolic modification also reinforces the mechanical strength of soft polymer scaffolds, which has been confirmed as a decisive factor for the osteoblast-directed differentiation of MSCs. Furthermore, phenol-contained coatings demonstrated a potential to serve as a controller of drug release, making the phenol-modified scaffolds more intelligent. Nanoparticle was an emerging pattern of BTE scaffolds with a nano-scale size. The miniaturised size of these scaffolds brings an improved *in vivo* distribution for loaded phenols, and at the same time, the interactions between phenols and nanoparticles also avoid burst release and lower the phenolic toxicity.

Despite the numerous advantages that phenol-modified BTE scaffolds already have, there still exist several pressing issues. For instance, the specific mechanism of phenols on BTC autophagy remains unclear, while the opinions are still opposite to each other about phenols' effects on bone vascularization. These uncertainties of phenols could bring unexpected impacts to BTCs. Furthermore, as Naji Kharouf et al. have stated, the incorporation of phenols may decrease the mechanical strength of ceramic materials, which could result in fears of possible breakage of these fragile scaffolds *in vivo*. Accordingly, we propose several perspectives for the future development of phenol-modified BTE scaffolds. First of all, more investigations should be conducted to figure out the precise mechanism of phenols' actions on BTCs. Meanwhile, the interactions of phenols and BTE scaffold substrates are also supposed to be explored. These measures can increase the biosafety and adaptability of phenol-modified BTE scaffolds to bones. In the meantime, discovering new mechanisms can be favorable for fabricating novel scaffolds with innovative functions. Furthermore, given that phenols have an outstanding performance in drug loading and controlled release, more drugs (e.g., gene-based medicine) and stimuli-responsive structures could be introduced into phenol-modified BTE scaffolds to establish personalized and customized therapeutic systems. Last but not least, scaffolds in innovative forms (for example, nanoparticles) should be taken into consideration as well. Different from traditional BTE scaffolds, these unique-shaped scaffolds usually have higher specific surface area, more adequate drug exchange from inside to outside and more diversified approaches to drug delivery. With the synergy of phenols, they are promising to create new therapies for bone defect.

CRediT authorship contribution statement

Yuhang Chen: Conceptualization, Data curation, Investigation, Project administration, Visualization, Writing - original draft. **Weikang Gan:** Data curation, Formal analysis. **Zhangrong Cheng:** Formal analysis, Investigation. **Anran Zhang:** Software. **Pengzhi Shi:** Investigation. **Yukun Zhang:** Project administration, Supervision, Writing - review & editing.

Declaration of competing interest

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

Data availability

No data was used for the research described in the article.

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