Traditional Chinese medicine promotes bone regeneration in bone tissue engineering

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Abstract
Bone tissue engineering (BTE) is a promising method for the repair of difficult-to-heal bone tissue damage by providing three-dimensional structures for cell attachment, proliferation, and differentiation. Traditional Chinese medicine (TCM) has been introduced as an effective global medical program by the World Health Organization, comprising intricate components, and promoting bone regeneration by regulating multiple mechanisms and targets. This study outlines the potential therapeutic capabilities of TCM combined with BTE in bone regeneration. The effective active components promoting bone regeneration can be generally divided into flavonoids, alkaloids, glycosides, terpenoids, and polyphenols, among others. The chemical structures of the monomers, their sources, efficacy, and mechanisms are described. We summarize the use of compounds and medicinal parts of TCM to stimulate bone regeneration. Finally, the limitations and prospects of applying TCM in BTE are introduced, providing a direction for further development of novel and potential TCM.

Keywords: Traditional Chinese medicine, Bone tissue engineering, Bone regeneration, Scaffolds, Osteogenesis

Graphical Abstract

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Traditional Chinese medicine (TCM)

Role of TCM
TCM comprises natural products and extracts derived from herbs, animals, and minerals with effective biofunctions for maintaining health and treating disease. During decades, its use has been widespread globally [1–3]. As early as the Eastern Han Dynasty, the classical text on Chinese Medicine, Shen Nong’s Materia Medica (Shen Nong Ben Cao Jing), recorded the use of TCM in the treatment of diseases. Nowadays, TCM has been shown to play a crucial role in the prevention and management of diseases, such as cardiovascular disease, cancer, and diabetes [4–6]. TCM was considered a “miracle” drug for certain major diseases, such as artemisinin in malaria and arsenic trioxide in acute promyelocytic leukemia [7, 8]. Therefore, further understanding and expanding the use of TCM is necessary for continued developments in the field.

Classification of TCM
The classification of TCM is sophisticated and complex. From the ancient books and Pharmacopoeias, such as Shen Nong’s Materia Medica [9], Compendium of Materia Medica (Ben Cao Gang Mu) [10], Yellow Emperor’s Inner Canon and Treatise on Cold Damage, to the latest Chinese Pharmacopoeia [11, 12], the classification standard of TCM are still different. And some of the scholar different from the traditional classification in China, some scholars divided TCM into Alkaloids, Terpenoids, Flavonoids, Volatile Oils etc. based on the active components (Table 1). The classification of TCM in this review is based on the active components reported for application in bone tissue engineering (BTE) that promote bone formation, including flavonoids, alkaloids, glycosides, terpenoids, and polyphenols, among others. And the drug component has been shown in Table 2. The classification of TCM is significant for guiding clinical application and avoiding instability and unsafety caused by improper combination [13].

BTE
Bone remodeling and regeneration are continuous and dynamic physiological processes regulated by two cellular mechanisms, namely bone formation and resorption.
## Table 2 The basic information of TCM

| Category   | Components         | Structural forms | Molecular weight | Source          | Main function                                                                 | References |
|------------|--------------------|------------------|------------------|-----------------|-------------------------------------------------------------------------------|------------|
| Flavonoids | Icariin            | ![Icariin structure](image1) | 676.67           | *Epimedium* species | Treatment of fractures, joint disease, and gonadal dysfunctions               | [31, 32]   |
|            | Icaritin           | ![Icaritin structure](image2) | 386.4            | *Epimedium* species | Osteoprotective effect, neuroprotective effect, cardiovascular protective effect, anti-cancer effect, anti-inflammatory effect, and immune-protective effect | [33]       |
|            | Hydroxy safflower yellow A | ![Hydroxy safflower yellow A structure](image3) | 612.53           | *Safflower* | Cardiovascular protection, coronary heart disease treatment and capillary angiogenesis, blood circulation and dispersing blood stasis | [34–38]   |
|            | Xanthohumol        | ![Xanthohumol structure](image4) | 354.4            | *Humulus lupulus* | Stimulate osteogenic differentiation, anti-inflammatory, and inhibits osteoclastogenesis | [39–41]   |
|            | Kaempferol         | ![Kaempferol structure](image5) | 286.23           | *Kaempferia galanga* | Osteoporosis, diabetes, obesity, immune regulation, antiviral, and antidepressant treatments | [42–45]   |
|            | Cuscuta chinensis Lam. | ![Cuscuta chinensis Lam. structure](image6) | Not applicable (NA) | *Kaempferia galanga* | Osteoporosis treatment                                                        | [45]       |
|            | Baicalin           | ![Baicalin structure](image7) | 446.36           | *Radix Scutellariae* | Antioxidant, antiapoptotic, and immunoregulatory activities with minimal side-effects | [46, 47]   |
| Category | Components | Structural forms | Molecular weight | Source | Main function                                                                 | References |
|----------|------------|------------------|------------------|--------|-------------------------------------------------------------------------------|-----------|
| Baicalein| Baicalein  | ![Baicalein](image) | 270.24           | Radix Scutellariae | Antioxidant, antiapoptotic, and immunoregulatory activities with minimal side-effects | [46, 47]  |
| Naringin | Naringin   | ![Naringin](image) | 580.53           | Tomatoes, grapefruits, and many other citrus fruits | Anti-inflammatory, antiapoptotic activities, and have therapeutic potential cancer, cardiovascular disease, diabetes, and oral disease | [48–50]  |
| Hesperetin| Hesperetin | ![Hesperetin](image) | 302.28           | Chenpi   | Antioxidant, anti-inflammatory, and anti-carcinogenic effects                   | [51]      |
| Quercetin| Quercetin  | ![Quercetin](image) | 302.24           | Quercetum, fruit and vegetables | Anti-inflammatory, anti-viral, anti-oxidant, anti-cancer properties, osteogenesis and angiogenesis | [52, 53]  |
| Silymarin| Silymarin  | ![Silymarin](image) | 482.44           | Silybum marianum | Hepatoprotective effects, anti-viral, anti-Parkinson, anti-Alzheimer effects, anti-cancer and anti-inflammatory | [54, 55]  |
| Category  | Components | Structural forms | Molecular weight | Source          | Main function                                                                 | References |
|-----------|------------|------------------|------------------|-----------------|-------------------------------------------------------------------------------|------------|
| Alkaloids | Tetrandrine| ![Tetrandrine](image) | 622.76           | *Stephania tetrandria* | Anti-inflammatory, immunosuppressant, anti-allergic effects, anti-oxidant, anti-diabetic and anti-microbial | [56, 57]   |
|           | Berberine  | ![Berberine](image) | 336.36           | *Rhizoma coptidis* | Diabetes, anti-inflammatory, anti-cancer therapies, lowering of blood lipids and promote bone formation | [58–60]   |
| Glycosides| Ginsenoside Rg1 | ![Ginsenoside Rg1](image) | 801.01           | Ginseng          | Cell proliferation and differentiation, anti-apoptosis, and anti-inflammation | [61]       |
|           | Ginsenoside Rb1 | ![Ginsenoside Rb1](image) | 1109.31          | Ginseng          | Osteogenesis                                                                  | [62]       |
| Terpenoids| Ursolic acid| ![Ursolic acid](image) | 456.70           | Fruits and vegetables | Anticancer, antioxidant, and other pharmacological effects                     | [63]       |
The loss of bone tissue can occur following an accident, trauma, cancer, and congenital malformation. Although bone remodeling and regeneration is a lifelong process, a bone defect, especially a large one, severely affects the function of the defunct area and quality of life due to the limited self-repair capacity of bone tissue and some inevitable side effects after surgery [15, 16]. Currently, the clinical “gold standard” for bone transplantation and reconstruction is autogenous bone grafts; however, the risk of donor site morbidity, limited graft supply, and bone formation delay must be seriously considered [17, 18]. To address naturally arising difficulties, BTE has been applied to provide a cell-friendly microenvironment for defect repair and tissue regeneration. BTE is an interdisciplinary field that combines the principles of engineering and biology to develop biological substitutes for restoring, maintaining, or improving bone tissue function [19, 20]. BTE has been applied in the treatment of large sections of bone tissue are absent, including traumas, bone cancer tumor resection, congenital malformation, and debridement of infected bone tissue [21].

The ideal characteristics of BTE including non-immunogenic, biocompatibility, controllable, readily available and have the mechanical properties similar to the natural tissue material, and possess suitable structure, architecture, and pore sizes for cells survival and activity [22, 23]. The advent and development of BTE brought about promising approaches for bone regeneration by ways of including the three key factors, namely (1) cells, (2) scaffolds, and (3) growth factors [24–26].

### Table 2 (continued)

| Category | Components | Structural forms | Molecular weight | Source | Main function | References |
|----------|------------|------------------|------------------|--------|---------------|------------|
| Polyphenols | Resveratrol | ![Resveratrol](image) | 228.25 | Veratrum grandiflorum O. Loes | Mediating inflammation, tumorigenesis, and cardioprotective effects | [64–66] |
| Curcumin | ![Curcumin](image) | 368.39 | Curcuma long L. | Anti-oxidant, anti-inflammatory, and anti-cancer effects | [67] |
| Epigallocatechin gallate | ![Epigallocatechin gallate](image) | 458.38 | Camellia sinensis L. | Anti-oxidant and anti-inflammatory effects | [68] |

### The application of TCM in BTE

The integrate TCM with BTE has a unique advantage in bone regeneration. Oral administration is the typical route for drug delivery, but the drawbacks such as first-pass metabolism would reduce the drug efficacy [69], while the topical delivery would prevention of first pass effect by liver and gut enzymes [70, 71]. To achieve successful and satisfactory therapeutic results, oral delivery requires overcoming the challenges by increasing the permeability of the intestinal epithelial membrane, inhibiting the degrading enzymes or protecting therapeutic by encapsulation [72], while the topical delivery can avoid this problem. Besides, the side effects of large doses of drugs have not been fully elucidated. At present, some drugs, such as BMP-2 and PTH, can be combined with BTE to promote bone defect healing. However, this may lead to extensive spread and subsequent accumulation in different organs, and further induce negative systemic side effects. Meanwhile, the production of these medicines are expensive [73]. Although the systemic administration of TCM shows low toxicity and side effects, it usually takes effect slowly. Therefore, regional TCM may provide a suitable alternative to TCM therapy. By integrating TCM with BTE, the BTE could act as a delivery carriers, and the topically-applied drug cannot only reach
the interior target tissue with a greater bioavailability, but also prolong residence time as well as sustain drug release [74]. At the same time, TCM combined with BTE can improve its mechanical properties, such as Young's modulus, compressive strength, hydrophilicity [75, 76].

Bone has the capacity of self-renewal; nevertheless, bone tissue regeneration remains a challenge [77]. The different types of TCM summarized here promote bone formation via multiple mechanisms and targets (Fig. 1), for instance, regulating the process of cell proliferation, osteogenesis and mineralization; chondrogenesis; angiogenesis; osteoclastogenesis; adipogenesis; and anti-inflammatory, anti-oxidant, anti-bacterial, and anti-apoptosis (Fig. 2).

**Proliferation, osteogenesis and mineralization**

Traditional Chinese medicine (TCM) has been praised in the world of medicine due to its effects in promoting cell proliferation, regulating bone metabolism, etc. [78], as shown in Table 3. Based on the variety of biomaterials, the use of TCM exhibits great biocompatibility and low cytotoxicity to the cells seeded on the biomaterial, even at extremely high concentrations, as shown by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide (MTT) assay and cell counting Kit-8 (CCK-8) assay [76, 79–82]. Icariin loaded PHBV scaffold significantly promoted the proliferation of human osteoblast-like MG-63 cells and the pre-osteoblast MC3T3-E1 cells in a concentration-dependent manner, as shown by Alamar blue assay, and the enhanced cellular proliferation results were due to the upregulating expression of BMP-2, BMP-6, BMP-7 and BGN [83]. Resveratrol and Ang-2 combined with PEGDA/TCS hydrogel showed a good cytocompatibility, and cell density in the resveratrol group was significantly higher than that in the control groups in a hypoxic environment, which was verified by the proliferation marker Ki67 via WB assay [84]. In addition, in the epigallocatechin gallate loaded gelatin scaffold, the chemical modification by epigallocatechin gallate would mitigate MMP-2 and -9 expression, thus slowing down the degradation of gelatin scaffold [85].
Except the low-cytotoxicity of TCM, which provided the basic condition for the application of TCM in BTE, TCM could also directly stimulate osteogenesis. Most studies adopted the rat calvarial bone defect models, while other studies also used tibial plateau defects model, rabbit bilateral thigh muscles model, rabbit lateral femoral condyle model, rat tibial ostectomy model, etc. [86–90]. The results show that more new bone formation and mineralization was found in the center and periphery of the bone defect area after filling with icariin-loaded bioactive scaffold, which attribute to the upregulating of osteogenic-related factors, such as RUNX2, ALP, OCN, COLI, BSP and OPN [76, 86, 91–94]. Besides, other TCM combined with different scaffold materials have similar effects, for instance, icaritin [88, 95], hydroxy safflower yellow A [96], kaempferol [97, 98], naringin [99, 100], quercetin [101–103], silymarin [104, 105], berberine [58, 90, 106], ginsenoside [62, 107], resveratrol [108–110], curcumin [111], and epigallocatechin gallate [112–115]. The rat calvarial defect almost completely repaired with physiological integrity at 16 weeks in the PLGA scaffold incorporated with gelatin, alendronate, and naringin groups, and this might owing to the inhibitory impact of alendronate on osteoclasts and the positive effect of naringin on osteoblasts, the PLGA + Gelatin/ALD/NG scaffold had a high potential for bone repair, as shown by upregulating BMP-2, OSX, OPN, BSP, COLI, OCN and calcium content, and inhibiting TRAP [116]. BMP family possess diverse biological functions during osteogenic differentiation, and including the maintenance of normal bone and bone regeneration. After the treatment of TCM loaded scaffold, BMP-2 and BMP-4 were significantly increased [58, 87, 96, 107, 111, 116–118]. Some of the research has demonstrated the mechanism under the TCM promoting bone regeneration. Baicalin/baicalein loaded Ca-polyP particles rises the intracellular calcium level through activation of the phospholipase C. Meanwhile, both flavones upregulated the expression of the osteoblast calcium efflux channel, the plasma membrane Ca2+-ATPase (PMCA), and the expression of ALP, which promotes bone mineralization [119]. Naringin-inlaid composite silk fibroin/hydroxyapatite scaffold had no effect on PI3K and Akt expression but strongly promoted PI3K phosphorylation compared to the control groups, indicating that naringin increased PI3K and Akt activity for stimulating osteogenic differentiation [49]. Using a
| Active components | Biomaterials | Experimental models | Efficacy | References |
|-------------------|-------------|---------------------|----------|------------|
| Icariin           | SF/SBA15    | Rat BMSC (rBMSC), 38.4 µM | Up-regulating RUNX2, ALP, OCN, and COLI | [94] |
|                   | SF/PLCL nanofibrous membrane | rBMSC, 10^{-5} mol/L; rat calvarial defects model | Up-regulating ALP activity | [76] |
| PLGA microspheres | rBMSC, 4 x 10^{-3} M; rat calvarial defects model | Up-regulating RUNX2, ALP, OCN, COLI, and OPN | [125] |
| Col/PCL/HAp composite scaffolds | rBMSC; rabbit tibial plateau defects model | Up-regulating ALP, COLI, OCN, and OPN | [86] |
| CS-modified halloysite nanotubes | hASCs, 10^{-5} M; | Up-regulating ALP | [79] |
| CS/nHAp           | Osteoblast  | N/A                 |          | [80] |
| PCL/Gel           | MC3T3-E1; 0.05 wt% | Up-regulating ALP, OCN, COLI, and calcium content | [91] |
| PLGA/TCP          | MC3T3-E1, 0.32%; SAON rabbit distal femur defect model; | Up-regulating BSP, OCN, and ALP | [92] |
| TCP               | Ros17/28, 5 x 10^{-3} M | Up-regulating ALP | [93] |
| PHBV scaffolds    | MC3T3-E1, MG-63, 25 mg/mL | Up-regulating BGN, BMP-2, BMP-6, and BMP-7 | [83] |
| BioCaP            | MC3T3-E1, 5 mg/L; rat calvarial defects model | Up-regulating ALP, OCN, RUNX2, BMP-2, and COLI | [87] |
| ECM-SIS           | MC3T3-E1, 10^{-5} M; mouse calvarial defect model | Up-regulating ALP, BSP, OCN, and BMP-4 | [117] |
| Icariin           | PLGA/TCP    | Rabbit BMSC, 0.74 g/kg; rabbit bilateral thigh muscles model | Up-regulating ALP and calcium deposition | [88] |
|                   | PLGA/TCP    | Rabbit BMSC, 1.4 x 10^{-5} M; | Up-regulating COLI, ALP, OCN and calcium deposition | [95] |
| Hydroxy safflower yellow A | BG | rBMSCs, HUVECs; rat calvarial defects model | Up-regulating RUNX2, OPN, OCN, ALP and BMP-2 | [96] |
| Xanthohumol       | HA-g-PLLA   | MC3T3-E1, 5, 10, 20 wt% | N/A | [81] |
| Kaempferol        | TiO₂        | rBMSC; rat femur defect | Up-regulating RUNX2, OCN, ALP, OPN and ON | [97] |
| Zn                | MG-63, 25 µM; Zebrafish model | Up-regulating RUNX2, COLI, ALP, OCN, and ON | [98] |
| Baicalin and baicalein | Ca-polyP | Primary human osteoblasts, 3 µg/mL | Up-regulating calcium, calcium efflux channel, PMCA and ALP | [119] |
| Naringin          | SF/HAp      | hUCMSCs, 0.1 wt%; rabbit femoral distal bone defect | Up-regulating ALP, RUNX2, OSX and COL1A and promoting AKT and PI3K phosphorylation | [49] |
|                   | microsphere/SAIB hybrid depot | Primary osteoblasts, 4% w/w; mouse calvarial defect model | Up-regulating ALP, RUNX2 and OCN | [99] |
| CS                | UMR106, 5 wt%; | Up-regulating ALP | [100] |
| PLGA/PDLLA        | MC3T3-E1, 7 wt%; | N/A | [82] |
| PLGA              | Rat calvarial defects model | Up-regulating BMP-2, OSX, OPN, BSN, COLI, OCN and calcium content | [116] |
| Hesperetin        | Gel         | hMSC, 1 µM; rat tibial osteotomy model | Up-regulating RUNX2, ALP, OCN and COLI and promoting ERK and Smads-1/5/8 phosphorylation | [89] |
| Active components | Biomaterials | Experimental models | Efficacy | References |
|-------------------|--------------|---------------------|----------|------------|
| **Quercetin**     | Ti           | hMSCs, 64 ± 10 and 842 ± 361 nmol | Up-regulating ALP activity and calcium content | [126] |
|                   | DC/HAp       | Rabbit BMSCs, 25 μM; rat calvarial defect model | Up-regulating RUNX2, OCN, and COLI | [101] |
|                   | PLLA         | MC3T3-E1, 200 μM | Up-regulating RUNX2, ALP, OCN, and COLI | [102] |
|                   | MSCS/PCL     | Wharton’s jelly MSC, 2% | Up-regulating calcium deposit | [127] |
|                   | Decellularized goat-lung scaffold | BMSC, 100 μM | Up-regulating ALP and calcium deposits | [128] |
| **Ti**            | DC/HAp       | hUCMSCs, HGF, 50 nM | Up-regulating RUNX2, COL, OCN, and ALP | [103] |
|                   | DC/HAp       | rBMSCs, 100 μM; rat calvarial bone defect model | Up-regulating RUNX2, COLI, and OCN | [104] |
|                   | PLA/Carbon nanotubes | Wharton’s jelly MSCs; rat calvarial bone defect model | Up-regulating ALP | [105] |
| **Silymarin**     | Zn           | C3H10T1/2, MG-63, 60 μM | Up-regulating RUNX2, COLI, and COLI | [104] |
|                   | Alginate/Gel | C3H10T1/2, 20, 50, 100 μM | Up-regulating ALP and OCN | [90] |
| **Silibinin**     | N/A          | DC/HAp | Up-regulating RUNX2, OCN, and COLI | [115] |
|                   | N/A          | DC/HAp | Up-regulating RUNX2, COLI, OCN, and COLI | [115] |
|                   | N/A          | DC/HAp | Up-regulating RUNX2, OCN, and COLI | [115] |
| **Berberine**     | PCL/COL      | DPSCs, 50 μg/mL; rat calvaria defects model | Up-regulating ALP, BMP-2, COLI and RUNX2 | [58] |
|                   | PCL/PVP-MC/CS bilayer membrane | MC3T3-E1, 10 μM; rat femur defect model | N/A | [106] |
|                   | Negatively charged O-carboxymethyl chitosan microspheres | MG-63, rBMSCs; rabbit lateral femoral condyle model | Up-regulating ALP and OCN | [90] |
| **Ginsenoside Rg1** | SF/PCL      | MC3T3-E1, HUVECs, 5% w/w | Up-regulating ALP, BMP-2, RUNX2 and OCN | [107] |
| **Ginsenoside Rb1** | MSCS/PCL    | hDPSCs, 5% v/v; rabbit femoral defect model | Up-regulating ALP, OPN and OCN | [62] |
| **Ursolic acid**  | MBG/CS porous scaffolds | hBMSCs, MC3T3-E1, 5 μM; rat calvarial defect model | Up-regulating ALP, COLI, RUNX2 and BMP-2 and promoting Smad1/5 phosphorylation | [118] |
| **Resveratrol**   | PEGDA/TCS hydrogel | rBMSCs, HUVECs, 800 μM; rat tibia defect model | Up-regulating Ki67, RUNX2, OPN, and calcium content | [84] |
|                   | PLGA microsphere | hMSCs, hTHP-1 monocytes, 25 μM | Up-regulating ALP, OCN and calcium content | [108] |
|                   | SLNs/GelMA   | rBMSCs, 0.02% w/v; rat calvarial critical-size defect model | Up-regulating ALP, OCN, RUNX2 and OPN | [109] |
|                   | PLA/OMMT     | hASCs, 0.1 wt% | Up-regulating ALP, OCN and OPN | [110] |
| **Curcumin**      | PCL          | MC3T3-E1, 1 wt% | Up-regulating RUNX2, ALP, BMP-2, OCN, and OPN | [111] |
| **Epigallocatechin gallate** | Ti-6Al-4 V  | hADSCs, Raw 264.7, 0.1 0.5, 1 mg/ml; rabbit tibia defect model | Up-regulating calcium content, RUNX2, OSX, OCN, OPN | [112] |
|                   | PLLA         | hADSCs, Raw 264.7, 1 mg/ml; mouse calvarial defect | Up-regulating ALP, RUNX2, and OPN | [113] |
|                   | Gel sponges  | UMR106, 0.07 mg; rat calvarial defects model | Down-regulating MMP-2, and MMP-9 | [85] |
|                   | POSS         | MC3T3-E1, 6 wt% | Up-regulating ALP | [114] |
|                   | DC/HAp       | Rabbit BMSC, 5 μM; nude mouse model | Up-regulating RUNX2, OCN, and COLI | [115] |
|                   | Gel sponges  | Rat calvarial defects model | N/A | [130] |
rat osteotomy model, hesperetin/gelatin sponge scaffold combined with mesenchymal stem cells resulted in accelerated fracture healing, which attributed to the activation of ERK and Smad1/5/8 signaling [89]. Similarly, Zn-silbinin complexes showed promising effects on osteoblast differentiation by regulating miR-590/Smad-7 signaling pathway [120], and ursolic acid loaded mesoporous bio-glass/chitosan porous scaffolds would promote the bone regeneration in rat calvarial defect model by stimulating Smad1/5 phosphorylation [118]. Both genipin and proanthocyanidins could act as a cross-linker, and promote the process of osteogenesis via upregulating the expression of RUNX2, OCN, OPN, and ALP [121–124].

### Chondrogenesis

Chondrocytes and the surrounding dense layers of extracellular matrix (ECM) form the cartilage [131]. Intramembranous ossification and endochondral ossification are two major processes to form new bone during bone repair [132]. It has been reported that endochondral ossification can be supported by biomaterials, and have a great bone regeneration in clinical [133]. Some of the TCM, for instance, icariin, resveratrol and epigallocatechin, can directly upregulate the expression of chondrogenic-related genes (Table 4). Icariin conjugated hyaluronic acid/collagen (HA/Col) hydrogel showed that the expression of SOX9, AGG, COL II, and COL X was remarkably up-regulated, and the matrix synthesis of sGAG and type II collagen was significantly enhanced [134]. In the rabbit osteochondral defect model, the icariin loaded biomaterials promoting the restoration of supercritical-sized osteochondral defects, as shown by the gross morphology examination and histological analysis, such as hematoxylin and eosin (H&E) and toluidine blue (TB) stained [134, 135]. Besides, icariin has the potential to promote stable chondrogenic differentiation of BMSCs without hypertrophy, and this would further accelerate the process of chondrogenesis [136]. Except upregulating the expression of SOX9, AGG, COLII and COLI in rabbit chondrocyte and BMSCs [137], Yu et al.
found that in the resveratrol–PLA–gelatin porous nano-scaffold, the expression levels of SIRT1, AKT and type II collagen proteins was increased significantly, while the expression levels of PI3K/AKT signaling pathway-related proteins, including VEGF, PTEN, Caspase9 and MMP13, was decreased significantly compared to the PLA–gelatin nano-scaffold without resveratrol, which was detected by the immunohistochemical staining. According to the H&E, Masson, Gomori, and Picrosirius red staining, the regenerated cartilage was the thickest, and more chondrocytes were observed with distribution and moderate morphology compared to the negative control groups [138]. The expression of cartilage-specific gene expression, such as $\text{COLII}$, $\text{SOX9}$ and $\text{ACAN}$ was detected by Real-time PCR assay, which showed similar trends as biochemical analysis that the epigallocatechin-loaded hyaluronic acid would promote chondrogenesis. $\text{COLI}$ and $\text{COLX}$, which are absent in healthy articular cartilage, was also examined and showed lower expression levels of these markers in epigallocatechin-loaded hyaluronic acid group [139].

**Angiogenesis**

Bone is a highly vascularized structure. The formation of blood vessel can stimulate and maintain bone cells activity, deliver nutrients and oxygen, and remove metabolites [141]. Notable, a subtype of blood vessel, type H vessels, was provided to be associated with bone formation [142]. TCM would mainly upregulate the expression of angiogenic-related genes, such as VEGF, ANG1, HIF-1α and CD31, to stimulate vascularization [143]. Liu et al. constructed an osteoporosis model in rats, and the osteogenic and angiogenic differentiation of bone mesenchymal stem cells (BMSCs) treated with icariin was evaluated. Real-time PCR analysis indicated that, similar to the expression of osteogenic genes, the expression of vascular endothelial growth factor (VEGF) and angiopoietin 1 (ANG1) mRNA was promoted by icariin, especially at 20 µM. CPC could act as a suitable icariin delivery system for repairing bone defects, and after implanted into nude mice, the extent of blood vessel growth in the icariin-loaded CPC groups was markedly greater than that in the CPC group. Besides, the systemic administration of icariin has an anti-osteoporotic effect that promotes bone defect repair [143]. Icariin could also induce the osteogenic differentiation in rat ASCs and stimulate the expression of VEGF, which would further promote the process of bone formation, as shown by SEM, micro-CT imaging, H&E and immunohistochemical staining [144]. A phytomolecule icaritin was regarded as a novel osteogenic exogenous growth factor, and a bioactive composite scaffold PLGA/TCP/icaritin was developed. The PLGA/TCP/icarin scaffold was implanted into the bone defect model, and the results of histological staining indicated favorable biocompatibility, rapid bioresorption and more new vessel growth in PLGA/TCP/icarin scaffolds in contrast to PLGA/TCP scaffolds [145]. Chung BH et al. constructed a similar complex scaffold, and PLGA/TCP/rBMSC, 1 µM; SAON rabbit both distal and proximal femur defect model MEK/ERK and PI3K/Akt/eNOS-dependent signal pathways [146, 147]. In the rabbit ulnar segmental bone defect model, the blood perfusion within defect sites was detected by dynamic MRI at weeks 2 and 4 post-surgery, which verified the PLGA/TCP/icaritin scaffolds induced significant blood vessel ingrowth into the pores of the implanted scaffold in the early stages of bone regeneration compared with that of the control scaffold [148]. Hydroxy-safflower yellow A was loaded into BG

| Active components | Biomaterials | Experimental model | Efficacy | References |
|-------------------|--------------|--------------------|----------|------------|
| Icariin           | CPC          | rBMSC, 20 µM; OVX rat calvarial defect model | Up-regulating VEGF and ANG1 | [143] |
|                   | SMC-PHBHhx scaffold | BMSC, $10^{-6}$ mol/L; rat calvarial defects model | Up-regulating VEGF, and FGF | [20] |
|                   | 455S Bioglass | rADSC, $10^{-7}$ mol/L; rat calvarial defects model | Up-regulating VEGF | [144] |
| Icaritin          | PLGA/TCP     | BMSC, BMC 0.052: 100 (powder weight to solution volume); rat calvarial defect model | Up-regulating OCN | [145] |
|                   | PLGA/TCP     | Rabbit ulnar segmental bone defect | N/A | [148] |
| Hydroxy safflower yellow A | BG | rBMSCs, HUVECs; rat calvarial defects model | Up-regulating HIF-1α | [96] |
| Silibinin         | Zn           | C3H10T1/2, MG-63; 60 µM; 3, 7 d | Up-regulating VEGF and ANG1 | [120] |
| Resveratrol       | PEGDA/TCS Hydrogel | rBMSCs, HUVECs, 800 µM; rat tibia defect model | Up-regulating CD31 | [84] |
|                   | PLGA microsphere | hMSCs, hTHP-1 monocytes, 25 µM | Up-regulating VEGF | [108] |
scaffolds by coating chitosan/sodium alginate film, and the expression levels of HIF-1α were more pronounced in a dose-dependent manner after 10 days induction in Hydroxy-safflower yellow A loaded groups, as shown by Western blot assay. Hydroxy-safflower yellow A contribute to osteogenesis and angiogenesis definitely, as well as the promotion of repair function and both in vivo and in vitro, the results of high-concentration of Hydroxy-safflower yellow A groups showed the best performance [96]. In the large tibial defect, resveratrol combined with ANG2 could promote new bone formation, and enhance density and size of new blood vessels by increasing autophagy to decrease ANG2 and hypoxia-induced apoptosis, maintaining the growth and proliferation in the endothelial cells, and upregulating the expression of CD31 in the bone defect area [84].

**Osteoclastogenesis**

The proper balance of osteoblasts and osteoclasts are essential in the maintenance of bone homeostasis [149]. Of these, osteoclasts, derived from haematopoietic lineage, are multinucleated cells involved in bone resorption. Macrophage colony-stimulating factor (M-CSF) and receptor activator of nuclear kappa B ligand (RANKL) is crucial for proliferation and differentiation of osteoclasts, respectively [149]. In the early stage of bone remodeling, osteoclast can remove the dying osteocytes and osteoblasts [150]. This can accelerate the process of bone remodeling. However, the dysregulating between osteoblast and osteoclast would lead to osteoporosis or heterotopic ossification [149]. Icariin and icaritin loaded biomaterials would downregulate the ratio of RANKL/OPG in BMSC and osteoclast, thus promoting osteogenesis by inhibiting osteoclastogenesis [143, 145]. After 7 days of cell culture, osteoclastic markers were evaluated, and quercitrin implant surfaces significantly decreased the expression of osteoclast related genes, including Trap, CalcR, Ctsk, H⁺ATPase, Mmp9 compared to controls. Besides, the functional osteoclastic markers Ctsk, H⁺ATPase and Mmp9 was significantly lower for quercitrin implant surfaces as well as the expression of Rankl in vivo [151]. Ursolic acid induced dose-dependent attenuation of titanium (Ti) particle-induced mouse calvarial bone loss, and decreased the number of tartrate-resistant acid phosphatase (TRAP)-positive osteoclasts, which attribute to inhibited the expression of NFATc1 in mRNA and protein level, primarily via the suppression of nuclear factor-kb (NF-kb) signaling, and partly through the suppression of c-Jun N-terminal kinase (JNK) signaling [152]. These results have been shown in Table 6.

**Adipogenesis**

Numerous studies have indicated a reciprocal relationship between osteoblastogenesis and adipogenesis, and adipogenesis-induction factors would inhibit osteoblastogenesis [153]. However, adipose-derived stem cells (ADSCs), similar to BMSCs, is an immune-privileged cell type with low immunogenicity, and can also differentiate into osteogenic and chondrogenic lineages [154, 155]. The using of icaritin loaded PLGA/TCP scaffold would prevent femoral head collapse in a bipedal SAON model, and this might partly attribute to the inhibiting adipogenic effect of icaritin. In SAON, the expression of adipogenic differentiation regulatory genes C/EBP-β, PPAR-γ and aP2group was control group by 15, 10 and 8 times. After treated with icaritin, the C/EBP, PPAR-γ and aP2 expression was reduced by 72%, 67% and 73%. Of these, C/EBP was required for the downstream proteins involved in adipogenesis, PPAR-γ was the key transcription factor in adipocyte differentiation, and aP2 was regarded as a terminal differentiation marker [156]. Icaritin loaded PLGA/TCP also demonstrated the down-regulating effect of PPAR-γ in rat calvarial defect model [145]. Cell-infiltratable and injectable gelatin hydrogels would be likely capable of mediating sustained delivery of icaritin to maintain a high-concentration in the

| Active components | Biomaterials | Experimental model | Efficacy | References |
|------------------|--------------|--------------------|----------|------------|
| Icariin          | CPC          | rBMSC, 20 µM; OVX rat calvarial defect model | Down-regulating RANKL | [143]         |
| Icaritin         | PLGA/TCP     | BMSC, BMC 0.052: 100 (powder weight to solution volume); rat calvarial defect model | Down-regulating RANKL/OPG | [145]         |
| Quercetin        | Ti           | RAW264.7, 1 mM; rabbit tibia model | Down-regulating Trap, CalcR, Ctsk, H⁺ATPase, MMP-9 and RANKL | [151]         |
| Ursolic acid     | Ti particle  | RAW264.7, BMMs, 5 µM; mouse calvarial bone defect model | Down-regulating NFATc1, NF-κb and JNK signaling | [152]         |
| Epigallocatechin | Ti-6Al-4-V   | hADSCs, Raw264.7, 0.1, 0.5, 1 mg/ml; rabbit tibia defect model | Down-regulating TRAP, CTSK, and RAW264.7 number | [112]         |
| PLLA             | ADSCs, Raw 264.7, 1 mg/ml; mouse calvarial defect | Down-regulating RAW264.7 number | [113]     |
long term, and the releasing of icaritin would inhibit the expression of adipogenic markers CEBPα and PPARγ after 7 and 14 days of culture, as shown by Real-time PCR and immunohistochemical staining [157]. The curcumin-loaded silk hydrogel exhibits an interconnected porous structure, and the results of adipogenic markers including PPAR-γ, LPL, FABp4, and Glut4, and the oil red O staining shows that film-associated curcumin accelerates hBMSC adipogenesis when the concentration of curcumin was more than 0.25 mg/mL, while adipogenesis of hBMSCs were inhibited when curcumin concentrations exceeded 5 µM [158]. Madhurakkat et al. found that Epigallocatechin gallate coating on nanofibers can serve as an anti-adipogenic platform by preventing differentiation of ADSCs into adipocytes via inhibiting the expression of LPL and PPAR-γ (Table 7) [113].

Others
Traditional Chinese medicines exhibit many biological activities, including anti-bacterial, anti-apoptotic, anti-inflammatory and antioxidant effects [159], and these could also contribute to the process of bone formation. Zinc silibinin complex exhibited antibacterial activity in a concentration-dependent manner. There was no significant change in bacterial growth with 1 g/mL of concentration whereas 10 g/mL concentration of Zn-silibinin complexes showed significant against E. coli (Gram-negative) and S. aureus (Gram-positive) strains compared to control, which would minimize the risk of bacterial infection post implantation and accelerate the augment of bone regeneration [120]. The berberine loaded negatively charged O-carboxymethyl chitosan microspheres possessed an ability to reduce the rate of infection caused by S. aureus, which can be ascribed to the burst release and diffuse of the berberine [38]. Except process the capacity of promoting osteogenesis, which was verified by the expression level of ALP and OCN, quercitrin-functionalized porous Ti-6Al-4 V implants also presented a great potential in decreasing bacterial adhesion and viability, which could decrease bacterial adhesion by 75% and produce a bactericidal effect [160]. For anti-apoptotic properties, the hBMSCs were co-cultured with ginsenoside Rg1-loaded alginate-chitosan microspheres groups. Ginsenoside Rg1 promotes hBMSC proliferation, accelerates differentiation into Nestin-, NSE- and GFAP-positive cells, and attenuates apoptosis through upregulating anti-apoptotic protein Bcl-2 and inhibiting pro-apoptotic protein Bax compare to the control groups [161]. Resveratrol–PLA–gelatin porous nano-scaffold has been shown to contribute to protect cartilage tissue. This can be attribute to the upregulating of SIRT1, which would delay the MMP13-induced decomposition of cartilage matrix, such as glycogen and II collagen, thus, the life of chondrocytes was prolonged [138].

In the bone defect model, the using of TCM, such as epigallocatechin gallate, resveratrol, ginsenoside Rb1 and baicalin, mainly attenuated the inflammation level by stimulating the expression of anti-inflammatory cytokine IL-10, and inhibiting the pro-inflammatory cytokines TNF-α, IL-1β, IL-6 [62, 108, 112, 114, 139, 162]. Resveratrol was incorporated into atelocollagen hydrogels to fabricate anti-inflammatory cell-free scaffolds, and then, the scaffolds were transplanted into the rabbit osteochondral defects. After implantation for 2, 4 and 6 weeks, the inflammatory related genes IL-1β, MMP-13, and COX-2 were remarkable decreased compared with the untreated defects, as shown by Real-time PCR. After 12 weeks, the osteochondral defects were completely repaired in scaffold groups, which was detected by immunohistochemical and glycosaminoglycan staining [137]. Tetrandrine loaded PLLA films possess sustained releasing behavior. The degree of inflammatory reaction for the implant with the tetrandrine loaded PLLA films was

| Active components | Biomaterials | Experimental model | Efficacy | References |
|-------------------|--------------|--------------------|----------|------------|
| Icaritin          | PLGA/TCP     | Rabbit BMSC, 3T3-L1, 10−6 M; SAON emu proximal femur defect model | Down-regulating C/EBP, aP2, PPAR-γ and lipid droplet | [156] |
|                   | PLGA/TCP     | BMSC, BMC 0.052: 100 (powder weight to solution volume); rat calvarial defect model | Down-regulating PPAR-γ2 | [145] |
|                   | Gel hydrogels | hMSC, 100, 200 nM; SAON rat femoral head defect | Down-regulating PPAR-γ and c-Src | [157] |
| Curcumin          | Silk hydrogel | hBMSC; 12.5 µM | Down-regulating PPAR-γ, LPL, FABp4 and Glut4 | [158] |
| Epigallocatechin gallate | PLLA | ADSCs, Raw 264.7, 1 mg/mL; mouse calvarial defect | Down-regulating LPL and PPAR-γ | [113] |
more moderate than control PLLA films in 4, 12 weeks after operation, due to tetrandrine maintained lower levels of inflammatory factors, such as NO, TNF-α, IL-6, iNOS, COX-2, which suggesting that tetrandrine could regulate the mRNA and protein expression to reduce the inflammatory response in macrophages, and accelerate tissue regeneration [163]. Huang AQ et al. combined the well-known antioxidant epigallocatechin gallate into gelatin sponges, and then, the implanted complex would decrease intracellular ROS levels in macrophage cell lines, as shown by anti-4-hydroxynonenal staining, thereby partially inhibiting the expression of MMPs, and promote bone formation (Table 8) [85].

| Mechanism                          | Active components | Biomaterials                  | Experimental models   | Efficacy                                                                 | References |
|------------------------------------|-------------------|--------------------------------|-----------------------|--------------------------------------------------------------------------|------------|
| Anti-bacterial properties          | Silibinin         | Zn                              | C3H10T1/2, MG-63, 60 µM | E. coli (Gram-negative) and S. aureus (Gram-positive) strains             | [120]      |
| Anti-bacterial properties          | Berberine          | Negatively charged O-carboxymethyl chitosan microspheres | MG-63, rBMSCs; rabbit lateral femoral condyle model | S. aureus                                                               | [90]       |
| Anti-bacterial properties          | Quercetin          | Ti-6Al-4 V                      | MC3T3-E1              | S. epidermidis                                                           | [160]      |
| Anti-apoptotic properties          | Ginsenoside Rg1    | Alginate-CS microspheres        | hBMSC, 2 g             | Up-regulating Nestin, NSE, GFAP and Bcl-2 and down-regulating Bax       | [161]      |
| Anti-inflammatory properties       | Resveratrol        | PLA–Gel porous nano-scaffold    | Rat articular cartilage defect model | Up-regulating SIRT1                                                       | [138]      |
| Anti-inflammatory and anti-apoptotic properties | Baicalin          | TPGS polymeric micelles         | Rat gingival fibroblasts, 20 mg/mL; rat periodontal disease model | Down-regulating TNF-α, IL-1β, and the number of inflammatory cells | [162]      |
| Anti-inflammatory properties       | Tetrandrine        | PLLA                            | RAW 264.7, 20 mg; rat model | Down-regulating NO, TNF-α, IL-6, iNOS, and COX-2                       | [163]      |
| Anti-inflammatory properties       | Ginsenoside Rb1    | MSCS/PCL                        | hDPSCs, 5% v/v; rabbit femoral defect model | Up-regulating IL-1RA and down-regulating IL-1β | [62]       |
| Anti-inflammatory properties       | Resveratrol        | COL/PAA                         | Chondrocytes, BMSCs, 0.5%; rabbit osteochondral defects model | Down-regulating IL-1β and MMP-13 and COX-2 | [137]      |
| Anti-inflammatory properties       | Resveratrol        | PLGA microsphere                | hMSCs, hTHP-1 monocytes, 25 µM | Up-regulating IL-10 and down-regulating TNF-α and IL-6                  | [108]      |
| Anti-inflammatory properties       | Epigallocatechin gallate | Ti-6Al-4 V                      | hADSCs, Raw264.7, 0.1, 0.5, 1 mg/mL; rabbit tibias defect model | Up-regulating IL-10 and down-regulating TNF-α and IL-6                  | [112]      |
| Anti-inflammatory properties       | Epigallocatechin gallate | Hyaluronic acid                 | Chondrocytes, 50 µM; mouse osteoarthritis model | Down-regulating IL-1β and TNF-α                                         | [139]      |
| Anti-oxidant and anti-inflammatory properties | Epigallocatechin gallate | POSS                            | MC3T3-E1, 6 wt%       | Down-regulating IL-6                                                    | [114]      |
| Anti-oxidant and anti-inflammatory properties | Epigallocatechin gallate | Gel sponges                     | UMR106, 0.07 mg; rat calvarial defects model | Down-regulating 4-HNE                                                   | [85]       |
| Anti-oxidant properties            | Resveratrol        | PLA/OMMT                        | HASCs, 0.1 wt%         | N/A                                                                      | [110]      |
| Anti-oxidant properties            | Quercetin          | CS/COL hydrogel                 | hPDLS; 100 µM          | N/A                                                                      | [164]      |
| Anti-oxidant properties            | Epigallocatechin gallate | PLLA                           | ADSCs, Raw 264.7, 1 mg/mL; mouse calvarial defect | N/A                                                                      | [113]      |

**Limitations, prospects, and conclusions**

Although the efficacy of TCM in the treatment of bone regeneration and remodeling has been widely studied, the field is still in its infancy. First, the reliability of TCM is suspected. TCM is a unique Chinese health care system, covering a broad range of medical theories and practices. It has been used for maintaining health and disease treatment over 2000 years. In modern medicine, the use of western medicine has clear indications and contraindications, while TCM is usually applied based on experience. TCM has not be tested by modern scientific research methods, such as cohort studies, randomized controlled studies, and experimental studies. Thus, the
salvia miltiorrhiza pharmacological properties, not only mainly applied to enhance blood circulation and for cardiovascular disease treatment by inhibiting RANKL-induced ROS via the (Turcz.) Baill, is a promising medicine for osteoporosis.

catechu plant- and animal-derived, have not been thoroughly phytochemicals, while the proteins and peptides, both different from the control group [178].

was formed on the surface, which was not significantly -coated Ti sample, little apatite Salvia miltiorrhiza genesis via upregulation of the expression of VEGF [177].

because of its diovascular disease treatment [176, 177]. Because of its belongs to the via miltiorrhiza verified, as they may not play the same role in BTE. Sal -

efficiency of TCM in bone regeneration must be further promoting osteoblast development [175]. However, the by activating and translocating of β-catenin nuclei, thus promoting the process of bone remodeling and regenera -

tion. Schisandrin A, isolated from Schisandra chinensis (Turcz.) Baill, is a promising medicine for osteoporosis treatment by inhibiting RANKL-induced ROS via the overexpression of nuclear factor erythroid 2-related factor 2 (Nrf2), suppressing the differentiation of osteoclasts [173]. Gastrodin, extracted from Gastrodia elata Blume, could reduce IL-1β-induced apoptosis in chondrocytes and attenuate the release of inflammatory mediators IL-6 and TNF-α, thus ameliorating rat cartilage degeneration [174]. Morin, a flavonoid derived from old fustic and osage orange trees, stimulates the Wnt pathway by activating and translocating of β-catenin nuclei, thus promoting osteoblast development [175]. However, the efficiency of TCM in bone regeneration must be further verified, as they may not play the same role in BTE. Salvia miltiorrhiza belongs to the Lamiaceae family and is mainly applied to enhance blood circulation and for cardiovascular disease treatment [176, 177]. Because of its pharmacological properties, Salvia miltiorrhiza not only promotes bone formation by regulating ALP, OCN, OPG, and RANKL expression, but also by stimulating angiogenesis via upregulation of the expression of VEGF [177]. In the Salvia miltiorrhiza-coated Ti sample, little apatite was formed on the surface, which was not significantly different from the control group [178].

Third, most research was conducted on plant-derived phytochemicals, while the proteins and peptides, both plant- and animal-derived, have not been thoroughly researched due to large quality difference from batch to batch. Although the development of recombinant technology can solve this problem to a certain extent, few proteins and peptides have been investigated [179]. Ling Zhi-8, purified from Ganoderma lucidum, is an immunomodulatory protein consisting of 110 amino acid residues. Ling Zhi-8 is a promising anti-osteoporosis drug for both preventive and therapeutic effects, which can regulate RANK/ RANKL/OPG signaling and inhibit the level of c-Fos and NFATc1, two key target genes of the osteoclast [180, 181]. In a standardized nasal bone defect, the polyurethane (PU)-based material was filled, and a higher bone volume was observed in the Ling Zhi-8-treated sample, although it was not as strong as BMP-2-treated sample [182]. Thus, the protein and peptide related research is promising. Not only proteins, but generally animal-derived TCMs were largely neglected due to slow and expensive research procedures, unstandardized material bases, and unclear active components [12]. Some of the animal-derived TCMs have been applied in BTE, such as Colla Cornus Cervi and Colla Plastri Testudinis. Further, other animal-derived TCMs may also have potential in bone regeneration. Kangfuxin, extracted from Periplaneta americana, has been verified in the mechanism against osteoporosis, as it accelerates bone formation through stimulating osteoblasts and HUVECs activities, while decreasing bone absorption by inhibiting osteoclast activities [183]. The kangfuxin-coated alginate/carboxymethyl CS sponge exhibits excellent antibacterial, cytocompatibility, and rapid hemostasis effects, and stimulates wound healing [1]. Furthermore, there are even fewer studies on mineral-derived TCM in bone regeneration. Therefore, TCMs that we investigated are only the tip of the iceberg, and which of them may become the “artemisinin” in bone tissue engineering is subject to further research.

With the modernization of TCM and the development of analytical and detection techniques, TCM has gradually transformed from an experience-based to an evidence-based medicinal system. The combination of TCM with “-omics”, such as metabolomics [184], microbiome [185], proteomics [186], and herbgenomics [187], can elucidate the mechanism and molecular targets of TCM, and further promote the development of TCM in the direction of precision medicine. In summary, TCM is a promising therapeutic method both in bone regeneration and BTE. This review provides a reference for the research of TCM for the application in BTE.

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Authors’ contributions
YG and YZF: Conceptualization, Supervision, Funding acquisition, ZRG, YQZ and JZ: Writing—Original Draft; ZRG and YG: Writing—Review & Editing; YHZ, QY and YC: Software, LT, SHZ, MAD: Supervision; YF, JH and ZYOT: Methodology. All authors read and approved the final manuscript.

Declarations

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

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