Evolving Roles of Natural Terpenoids From Traditional Chinese Medicine in the Treatment of Osteoporosis

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Osteoporosis (OP) is a systemic metabolic skeletal disease which can lead to reduction in bone mass and increased risk of bone fracture due to the microstructural degradation. Traditional Chinese medicine (TCM) has been applied in the prevention and treatment of osteoporosis for a long time. Terpenoids, a class of natural products that are rich in TCM, have been widely studied for their therapeutic efficacy on bone resorption, osteogenesis, and concomitant inflammation. Terpenoids can be classified in four categories by structures, monoterpenoids, sesquiterpenoids, diterpenoids, and triterpenoids. In this review, we comprehensively summarize all the currently known TCM-derived terpenoids in the treatment of OP. In addition, we discuss the possible mechanistic-of-actions of all four category terpenoids in anti-OP and assess their therapeutic potential for OP treatment.

Keywords: osteoporosis, traditional Chinese medicine, terpenoids, osteoblast, osteoclast

INTRODUCTION

As a systemic skeletal disease, Osteoporosis (OP) is characterized by increased risk of bone fragility, chronic pain, and even disability, leading to decreased life quality. Especially, OP strongly affects postmenopausal women and elderly population. About 30-50% of women and those who are more than 70 years old suffer from OP-induced fractures throughout their lives (1–3). In health condition, osteoblasts (OBs, bone-forming cells) and osteoclasts (OCs, bone-resorbing cells) form a balance for bone homeostasis. The lack of OB function or over-activated OC status will disturb the balance and induce OP.

In recent years, there has been a growing interest in traditional Chinese medicine (TCM) for the treatment of OP, such as Liu-Wei-Di-Huang Wan (formula), Morindae Officinalis Radix (herb), Longspur epimedium glycoside (natural product) (4). TCM has accumulated extensive experience for thousands of years and owns fewer adverse effects during a long-term usage comparing to some chemically synthesized medicines (5). Chinese herbal medicines usually play their therapeutic roles through a “multi-components, multi-targets, multi-pathway” mode, which is compatible with the multifactorial nature of OP. Plenty of evidence suggest that targeting OCs with TCM is an efficient strategy for the treatment of OP (6–8).
According to the theory of TCM on the pathogenesis and symptoms of OP, the kidney stores essence, turns it into bone marrow, nourishes bones to strengthen the skeleton, and promotes bone growth and repair. Therefore, ‘kidney deficiency’ is regarded as the underlying cause of all skeletal pathologies (9, 10). Many classic and empirical formulas of TCM used to tonify the kidney are clinically applied in OP treatment, TCMs like Liu Wei Di Huang Wan, Qing E Wan, Jiawei Yanghe Decoction, Er Zhi Wan, Qiangji Jianli Yin, Zuo Gui Wan, Rongji Tablets, and You Gui Wan showed excellent anti-OP efficacy through reinforcing the kidney (8). Modern pharmacological studies have shown that these classic formulas significantly inhibited OC formation and bone resorption, and promoted bone formation to increase bone mineral density (BMD) (8, 9). Moreover, many individual herbs that make up the formulas of TCM are beneficial for bone formation since they are bone-specific drugs for the treatment of bone fractures and bone loss diseases (11). *Rehmanniae Radix* has been clinically used for more than 3,000 years in Chinese medicine, which has an anti-OP effect through modulating the kidney and liver functions and improving blood circulation (12). Over 140 individual compounds have been isolated from *Rehmanniae Radix*, and iridoid glycosides (a kind of monoterpenoids) are vital for the anti-OP activity of *Rehmanniae Radix* (6).

Terpenoids are structurally diverse and may represent the most diverse source of essential chemotherapeutic drugs. They are isoprene units (C₅H₈)n-based nature products and are classified into monoterpenes, sesquiterpenes, diterpenes, triterpenes, and tetraterpenes. To date, more than 40,000 different terpenoids have been obtained in nature (13, 14). Terpenoids are also reported to have anti-inflammatory, anti-cancer, and neuroprotective effects, with beneficial effects on human health. Although the treatment of OP using TCM has a long history and natural terpenoids have been extensively studied for their therapeutic activities against bone resorption (15), less attention has been given to the whole series of terpenoids in the treatment of OP. Therefore, we here summarize anti-OP advances and molecular mechanisms of terpenoids isolated from TCM.

**NATURAL TERPENOIDS AGAINST OP**

Terpenoids are classified as monoter-, sesquiter-, diter-, triter-, and tetra-terpenoids according to different structures (Figures 1 and 2). Although few natural terpenoids exhibit genotoxicity or carcinogenicity based on epigenetic mechanism, most are beneficial to humans (15). Natural terpenoids from TCM have been reported to regulate OBs and OCs via different signaling pathways (concluded in Figure 3 and Table 1), such as nuclear factor-kB (NF-kB), Wnt/β-catenin, mitogen-activated protein kinases (MAPK), and receptor activator of nuclear factor-kB ligand (RANKL)/receptor activator of nuclear factor-kB (RANK). We will provide a comprehensive review of natural terpenoids from TCM and their potential in OP therapy.

**Monoterpenoids**

Sweroside, an iridoid glycoside obtained from *Cornus officinalis* Sieb. et Zucc. (Shan Zhu Yu in Chinese), is commonly used in TCM for treating OP in postmenopausal women or elderly men (93). Emerging evidences demonstrated that sweroside increased the proliferation and suppressed the apoptosis of human MG-63 cells and rat OBs (17). Yan et al. observed that sweroside effectively promoted OB differentiation in bone marrow mesenchymal stem cells (BMSCs) through hyperactivating the mechanistic target of rapamycin complex 1 (mTORC1)/pS6 signaling pathway (19). Additionally, sweroside treatment induced the mineralization of bone matrix via modulating the expression of bone morphogenetic protein (BMP)-2/core binding factor alpha 1 (CBF1)-mediated molecules in postmenopausal OP. Meanwhile, sweroside promoted the mineralization of MC3T3-E1 cells by activating p38 signaling pathway (16, 18). Swertiamarin, a structural analog of sweroside, is a secoiridoid glycoside extracted from *Enicostemma axillare* subsp. axillere (Gentianaceae) (94). It was evidenced that swertiamarin could promote OB differentiation and exhibit anti-inflammatory activity by regulating NF-kB/Inhibitor of kB (I kB) and Janus kinase 2 (JAK2)/signal transducer and activator of transcription 3 (STAT3) signaling pathways. In addition, swertiamarin treatment markedly reduced RANKL/RANK expression and elevated osteoprotegerin (OPG) level, showing an excellent anti-osteoclastogenic activity (20–22).

*Morinda officinalis* HOW (Ba Ji Tian in Chinese) has been continuously used for more than 2,000 years in China as a tonic to nourish the kidney, strengthen bones, and enhance immune function in the treatment of OP (95, 96). It has been reported that the root extracts of *Morinda officinalis* showed therapeutic effect by suppressing bone resorption and enhancing bone formation on OP rat model induced by sciatic neurectomy and ovariecotmy (97). He et al. observed that monotropein, a natural iridoid glycoside in the root extracts of *Morinda officinalis*, effectively attenuated lipopolysaccharide (LPS)- and ovariecotmy-induced bone loss, and reduced inflammatory responses in MC3T3-E1 cells via inhibiting the activation of NF-kB (23). Furthermore, monotropein showed anti-osteoporotic effect by increasing bone mineral content (BMC), BMD, bone volume fraction (BVF), and decreasing the levels of interleukin (IL)-1, IL-6 and soluble RANKL in the serum of ovariecotmyed (OVX) mice (25). Meanwhile, monotropein treatment attenuated oxidative stress and increased the proliferation of OBs (24, 25).

Catalpol, the major bioactive iridoid glycoside isolated from *Rehmannia glutinosa* (Gaertn.) Libosch. ex Fisch. et C. A. Mey. Root (Dihuang in Chinese), is clinically used for OP treatment in China (6). Meng et al. showed that catalpol suppressed RANKL-induced bone resorption in bone marrow-derived macrophages (BMMs) and RAW264.7 cells by reducing the ubiquitination of phosphatase and tensin homolog (PTEN), which subsequently inhibited the activations of NF-kB and protein kinase B (Akt) (26). Other reports also proved that catalpol treatment promoted the osteogenic ability of BMSCs and BMSC-dependent angiogenesis, partly via activation of JAK2/STAT3 axis and...
**Monoterpenoids**

- Paeoniflorin
- Bakuchiol
- Albiflorin
- Monotropein

- Catalpol
- Sweroside
- Swertiamarin

**Sesquiterpenoids**

- Dehydrocostus Lactone
- Costunolide

**Diterpenoids**

- Euphorbia Factor L1
- Abietic Acid
- Andrographolide
- Carnosic Acid

- Oridonin
- Crocin
- Kirenol

- Tanshinone IIA
- Tanshinone VI
- Triptolide

**FIGURE 1** Chemical structures of natural monoterpenoids, sesquiterpenoids and diterpenoids from TCM.
**FIGURE 2** | Chemical structures of natural triterpenes from TCM.
Wnt/β-catenin pathway (27, 28). Furthermore, Zhao et al. observed that catalpol could protect diabetic OP induced by high glucose treatment in MC3T3-E1 cells through regulating the migration and differentiation of OBs (29).

As a water-soluble monoterpene glucoside, paeoniflorin is the major bioactive components extracted from the root of *Paeonia lactiflora* Pall (98). In antiymin A treated osteoblastic MC3T3-E1 cells, paeoniflorin attenuated cytotoxicity via improving the mitochondrial function. In addition, paeoniflorin also increased the differentiation of MC3T3-E1 cells and inhibited oxidative stress induced by methylglyoxal in the same cell model (30, 33, 98). In rats fed on high-carbohydrate/high-fat (HCHF) diet, paeoniflorin exhibited multiple pharmacological activities to prevent hyperlipidemia-induced OP. Intriguingly, paeoniflorin increased the trabecular and cortical parameters, as well as width and length of femur. Simultaneously, paeoniflorin rescued OB differentiation and the proliferation activities of bone turnover markers (99). Xu et al. reported that paeoniflorin suppressed bone destruction in collagen-induced arthritis (CIA) and decreased OC differentiation in vitro by down-regulating the activation of NF-κB (31). Wang et al. demonstrated that paeoniflorin suppressed OC generation and promoted OB formation via regulating osteoclasts. Some terpenoids, such as andrographolide and tanshinone IIA, show anti-osteoporosis effect by modifying multi-targets. Arrows (↓) indicate activation of a factor or positive effect on indicated cell type, while inverted T marks (⊥) indicate inhibition or negative effect. Subclass of terpenoids is distinguished with different colors: monoterpoids (red), sesquiterpenoids (yellow), diterpenoids (blue), and triterpenoids (green).

Albiflorin, a monoterpene glycoside isolated from the roots of *Paeonia lactiflora* Pall., owns the ability to increase the differentiation of osteoblastic MC3T3-E1 cells (98). Kwang et al. found that albiflorin maintained mitochondrial function by reducing cytochrome c loss and cardiolipin peroxidation in MC3T3-E1 cells, which contributed to the inhibition of antimycin A-induced oxidative stress and toxicity (34). Another study showed that albiflorin treatment promoted the
| Category       | Compound                  | TCM               | Cells/in vivo model                                      | Mechanism                                                                 | Reference |
|----------------|---------------------------|-------------------|--------------------------------------------------------|---------------------------------------------------------------------------|-----------|
| Monoterpenoids | Sweroside                 | Comus officinalis | Human osteosarcoma cell line (SaOS-2); OVX mice       | Induced the mineralization of bone matrix via promoting BMP2/CBFA1         | (16)      |
|                |                           |                   | Human MG-63 cells; Rat OBs                             | Promoted differentiation and inhibited apoptosis                           | (17)      |
|                |                           |                   | MC3T3-E1 cells; BMSCs; OVX mouse                       | Activated p38 signaling pathway                                           | (18)      |
|                |                           |                   | Rat fibroblast-like synoviocytes (FLS)                 | Hyperactivated the mTOR1/PS6 signaling pathway                             | (19)      |
|                |                           |                   | RAW 264.7 macrophage cells C57/BL6J BMSCs; Sprague    | Inhibited caspase 3, TNFa, IL-6, PGE2, COX-2, INOS, MMPs, p38 MAPKa and modulated RANKL | (20)      |
|                |                           |                   | Dawley rat neonates OBs; Freund’s Complete Adjuvant induced rat arthritis |blocked NF-κB pathway; Enhanced bone formation and blocked increased secretion of inflammatory cytokines| (21)      |
|                | Swertiamarin              | Enicostema axillare| Rat fibroblast-like synoviocytes (FLS)                 | Inhibited caspase 3, TNFa, IL-6, PGE2, COX-2, INOS, MMPs, p38 MAPKa and modulated RANKL | (20)      |
|                |                           |                   | BMSCs; OVX mouse                                       | Activated p38 signaling pathway                                           | (18)      |
|                |                           |                   | RAW 264.7 macrophage cells C57/BL6J BMSCs; Sprague    | Inhibited caspase 3, TNFa, IL-6, PGE2, COX-2, INOS, MMPs, p38 MAPKa and modulated RANKL | (20)      |
|                |                           |                   | Dawley rat neonates OBs; Freund’s Complete Adjuvant induced rat arthritis |blocked NF-κB pathway; Enhanced bone formation and blocked increased secretion of inflammatory cytokines| (21)      |
|                | Catalpol                  | Rehmannia glutinosa| BMSCs; RAW264.7 cells; C57/BL6 mice                    | Suppressed NF-κB and AKT signaling pathways                               | (26)      |
|                |                           |                   | BMSCs; Male Sprague-Dawley rats                        | Activated Wnt/β-catenin pathway.                                          | (27)      |
|                |                           |                   | BMSCs; SD female rats                                   | Activated JAK2/STAT3 axis                                                 | (28)      |
|                |                           |                   | MC3T3-E1 cells; Male ICR mice                          | Inhibited bone resorption via the OPG/RANKL pathway; enhanced bone formation by regulating IGF-1/P38/mTOR pathways | (29)      |
|                | Paeoniflorin              | Paeonia lactiflora| Mouse BM cells; Mice OC; RAW 264.7 cells; Male DBA/1 mice; Male C57/BL6 mice |Enhanced glyoxalase system and inhibited the glycation                     | (30)      |
|                |                           |                   | Primary human OBs; OVX rats Sprague-Dawley rats        | Suppressed NF-κB signaling pathway                                        | (31)      |
|                |                           |                   | Primary osteoblastic MC3T3-E1 cells                     | Activated PI3K signaling pathway                                         | (32)      |
|                |                           |                   | Murine osteoblastic MC3T3-E1 cells; Bone marrow cells   | Suppressed oxidative damage through protecting cytochrome c and cardiolipin | (34)      |
|                |                           |                   | MC3T3-E1 cells; Sprague Dawley rats femoral fractures | Activated BMP-2/Smad and Wnt/β-catenin pathway                            | (35)      |
|                | Bakuchiol                 | Psoralea coryliifla| Mouse BM cells; Mice OC; RAW 264.7 cells; Male DBA/1 mice; Male C57/BL6 mice |Up-regulated the Wnt signaling pathway                                    | (36)      |
|                |                           |                   | Primary human OBs; OVX rats Sprague-Dawley rats        | Inhibited NF-κB and NFAT signaling pathways                               | (37)      |
|                | Sesquiterpenoid           | Saussurea lappa    | Mouse OB MC3T3-E1 cells                                | Suppressed NF-κB signaling pathway                                         | (38)      |
|                | Costunolide               |                   | Mice BMcs                                              | Suppressed PI3K signaling pathway                                         | (39)      |
|                | Dehydrocostus lactone    |                   | Mice BMMs, BMSCs; RAW264.7 cells; OVX C57BL/6; BMSCs; | Suppressed RANKL-mediated c-Fos transcriptional activity                  | (40)      |
|                |                           |                   | Mice BMMs; Male C57BL/6 mice                           | Suppressed RANKL-mediated c-Fos transcriptional activity                  | (41)      |
|                | Euphorbia factor L1       | Euphorbia lathyris| Mouse MMcs; C57BL/6 male mice                          | Activated Wnt/β-catenin signaling pathway                                  | (42)      |
|                | Abietic acid              | Pimenta racemosa  | RAW 264.7 cell line; Mice BMMs; C57BL/6 male mice BMSC; |Attenuated c-Fos expression and NF-κB activation; activated Nrf2 signaling pathway | (43)      |
|                | Andrographolide           | Andrographis paniculata | Mouse BMMs; RAW 264.7 cells; OVX C57BL/6 mice MC3T3-E1 cell; OVX Sprague Dawley rats | Activated wnt/β-catenin signaling pathway                                  | (44)      |
|                |                           |                   | Mouse OB MC3T3-E1 cells                                | Suppressed NF-κB and AP-1 pathways                                        | (45)      |
|                |                           |                   | Mice BMcs                                              | Suppressed NF-κB and AP-1 pathways                                        | (46)      |
|                |                           |                   | Mice BMMs; OVX C57BL/6 female mice                     | Down-regulated the integrin b3, PKC-b, and Algl5 expression               | (47)      |
|                | Diterpenoids              | Morinda officinalis| Mouse BMcs; C57BL/6 male mice                          | Suppressed NF-κB and AP-1 pathways                                        | (48)      |
|                |                           |                   | RAW 264.7 cell line; Mice BMMs; C57BL/6 male mice BMSC; | Activated wnt/β-catenin signaling pathway                                  | (49)      |
|                |                             |                   | Sprague-Dawley rats                                    | Suppressed RANKL signaling pathway                                        | (49)      |

(Continued)
| Category | Compound | TCM | Cells/in vivo model | Mechanism | Reference |
|----------|----------|-----|---------------------|-----------|-----------|
| Carnosic acid | *Salvia officinalis* | RAW 264.7 cells; Mouse BMSCs; OVX Sprague-Dawley rats Mouse BMMs; C57BL/6 mice RAW 264.7 cells; Mouse BMMs; Female C57BJ/6L mice | Inhibited the NF-kB signaling pathway Attenuated NF-κB and ERK/MAPK signalling pathways Activated the Nrf2 and suppressed the NF-κB pathways | (50) (51) (52) |
| Crocin | *Crocus sativus* | RAW264.7 cells Mice BMMs; Murine macrophage cell line; RAW264.7 cells | Regulated glyoxalase, oxidative stress, and mitochondrial function Suppressed NF- B signaling pathway | (54) (55) |
| Kirenol | *Siegesbeckia orientalis* | Mouse BMMs; OVX C57BL/6 mice | Suppressed the NF-κB, PI3-kinase/Akt, and MAPK pathways, as well as the transcription factor NFATc1 | (55) |
| Tanshinone IIA | *Salvia miltiorrhiza* | Mouse BMSCs; Mouse BMMs; SD rats Activated Wnt11/β-catenin signaling pathways | Suppressed NF-κB signaling pathway | (57) |
| Tanshinone VI | *Salvia miltiorrhiza* | Mice BMMCs; RAW-264.7 cells; C57BL/6 mice | Activated the BMP and Wnt/β-catenin signaling pathways | (56) |
| Triptolide | *Tripterygium wilfordii* | Oligosaccharides (Ocs) | Inhibited the expression of c-Fos and NFATc1 | (59) |
| Oridonin | *Rabdosia rubescens* | Mouse BMSCs; OVX C57BL/6 mice | Suppressed the NF-κB, PI3-kinase/Akt, and MAPK pathways, as well as the transcription factor NFATc1 | (60) |
| Triterpenoids | *Bombax ciba* | UMR-106 cell; Female Wistar albino rats | Inhibited RANKL and up-regulated OPG expression in vitro | (66) |
| Alisol B 24-acetate | *Alismatis rhizoma* | Released Syk-mediated down-stream signals including PLC, ERK, and p38 MAPK, NF-κB, cPLA2, COX-2, and Ca2+ | Inhibited NFATc1 and c-Fos signaling pathway | (68) |
| Alisol C 23-acetate | *Ligustri lucidi* | Calvaria osteoblastic cell; Ocs; OVX rat | Inhibited RANKL-induced osteoclast differentiation and function | (69) |
| Ursolic acid | *Glycyrrhiza glabra* | Mouse osteoblastic MC3T3-E1 subclone 4 cells Mouse osteoblasts; Female C57BL/6 mice RAW264.7 cells RAW264.7 cells; Mouse BMMs;OVX C57BL/6J mice Male CSF1r-eGFP-KI mice and their wild type strain C57BL/6 | Activated MAP kinases and NF-κB signaling pathway Inhibited 11β-hydroxysteroid dehydrogenase type 1 enzyme (11β-HSD1) Suppressed NF-κB, ERK, and JNK pathway Inactivated NF-κB signaling Diminished the size of inflammatory osteolysis via the number of CXCR4+OCPs and TRAP+osteoclasts, decreased the senescence- | (70) (71) (72) (73) |

(Continued)
generation of OBs and expression of runt-related transcription factor 2 (RUNX2) through activating BMP-2/Smad and Wnt/β-catenin signaling pathways (35). Meanwhile, albinorin up-regulated the levels of various osteogenic genes, such as osteocalcin (OCN), osteopontin (OPN), osteonectin (OSN), bone sialoprotein (BSP), and AP. In femur fracture rat model, albinorin stimulated the expression of osteogenic genes in femoral tissue and promoted callus formation at the early stage during fracture recovery. Additionally, albinorin could increase the expression of bone-related genes (35). This finding suggested that albinorin motivated bone calcification, osteogenesis and bone formation, resulting in improving the fracture healing.

Bakuchiol is a prenylated phenolic monoterpene in the fruit of *Psoralea corylifolia* (L.) Medik (37, 100). And *Psoralea corylifolia* was used in TCM formulas to treat osteoporosis for a long history time (101). Recent researches indicated that bakuchiol treatment reduced bone loss through increasing Ca2+ and serum E2 concentrations, AP activity, and BMD, along with reduced inorganic P level (37). Li et al. found that bakuchiol significantly stimulated OB proliferation and differentiation (103). In addition, bakuchiol treatment prevented bone loss in OVX rats induced by estrogen deficiency and induced OB differentiation by up-regulating the Wnt signaling pathway (36).

Collectively, monoterpenoids can protect bone from erosion via targeting different signaling pathways. In OBs, catapol, albinorin, and bakuchiol can activate Wnt/β-catenin signaling pathway; paoniflorin and sweroside stimulate PI3K/Akt and MAPK signaling pathways respectively; swertiamarin inhibits RANKL/RANK signaling pathway; monotropein and swertiamarin suppress NF-κB signaling pathway. In OCs, catapol and paoniflorin depress NF-κB signaling pathway; bakuchiol enhances PI3K/Akt signaling pathway.

**Sesquiterpenoids**

Costunolide is sesquiterpene lactones derived from *Saussurea lappa* C.B. Clarke roots. A recent research showed that costunolide remarkably induced bone mineralization and differentiation and increased cell growth, AP activity, and collagen synthesis in osteoblastic MC3T3-E1 cells via targeting diverse key proteins, such as estrogen receptor (ER), phosphoinositol 3-kinase (PI3K), extracellular signal-regulated kinase (ERK), protein kinase C (PKC), mitochondrial ATP-sensitive K+ channel, p38, and c-Jun N-terminal kinase (JNK) (39). Moreover, Cheon et al. observed that costunolide

**TABLE 1 | Continued**

| Category          | Compound          | TCM                      | Cells/in vivo model                                                                 | Mechanism                                                                 | Reference |
|-------------------|-------------------|--------------------------|------------------------------------------------------------------------------------|---------------------------------------------------------------------------|-----------|
| Glycyrrhetinic    | Acid              | Mouse BMMs; RAW264.7     | associated secretory phenotype markers, and elevated the senescence-protective markers | Inhibited NF-κB and MAPK signaling pathways.                                | (78)      |
| Ginsenoside       | Rg1               | Mouse BMMs; Female C57BL/6 mice; OVX C57BL/6 female mice | Promoted the proliferation and differentiation of DPSCs into odontoblast-like cells by promoted the expression of anti-osteoporosis related genes | Inhibited MAPK and NFATc1 signaling pathways                              | (79)      |
| Betulinic Acid    | Pubescens         | Mouse BMMs; Female C57BL/6 mice; OVX mice | Activated BMP/Smad/Runx2 and β-catenin signal pathways                              | Inhibited bone resorption and reduced the number of multinucleated cells  | (81)      |
| Limonin           | Evodia             | Mouse BMMs; Mouse RAW 264,7 | Inhibited bone resorption and induced the number of multinucleated cells           | Promoted the p38-MAPK signaling                                            | (83)      |
| Norinlin          | Citrux junos      | Mouse BMMs; Mouse RAW 264,7 | Promoted the proliferation and differentiation of DPSCs into odontoblast-like cells by promoted the expression of anti-osteoporosis related genes | Suppressed NFATc1 and MAPK signaling pathways                                | (84)      |
| Diosgenin         | Diocorea nipponica | Mouse BMMs cells; RAW264.7 cells; LPS-induced bone loss mouse | Decreased the RANKL/OPG ratio                                                     | inhibiting the Akt signaling pathway                                       | (69)      |
| Dioscin           |                   | Mouse BMMs cells; RAW264.7 cells; LPS-induced bone loss mouse | Promoted osteoblasts proliferation and differentiation via Lrp5 and ER pathway     | (87)                                                             |
| Ophiopogonin D    | Ophiopogon japonicus | OBs MC3T3-E1 cells; RAW264.7 cells; OVX mouse Endothelium-specific Kit3 knockout mice | Reduced oxidative stress via the FoxO3α-β-catenin signaling pathway               | (88)                                                             |
| Cycloastragol     | Astragulus        | MC3T3-E1 cells           | Inhibited Krüppel-like factor 3 (KLF3)                                              | (89)                                                             |
| Hederagenin       | Hedera helix      | Mice BMMs; OVX mice      | Inhibited RANKL-induced bone resorption and OC generation, activated MAPK signaling pathway | (91)                                                             |
| Tubeimoside I     | Bolbostemma       | Mice BMMs; RAW 264,7 cells; Male SD rats | Down-regulated NF-κB signaling pathway                                              | (92)                                                             |
|                   | paniculatum       |                          |                                                                                    |                                                             |           |
suppressed RANKL-induced OC differentiation via suppressing c-Fos transcriptional activity without affecting c-Fos expression (40).

_Saussurea lappa_ C.B. Clarke has been used in clinic for decades as a TCM (104). Sesquiterpenes and sesquiterpene lactones are main bioactive constituent of this herb. As a member of sesquiterpene lactones, dehydrocostus lactone is extracted from the roots of _Saussurea lappa_ and has been reported to exert various pharmacological activities including anti-ulcer, anti-tumor, anti-inflammatory, and immunomodulation (42, 105). In mouse BMMs, dehydrocostus lactone attenuated the RANKL-dependent OC differentiation through modulating IκB kinase (IKK), JNK, nuclear factor of activated T cell cytoplasmic 1 (NFATc1), and nuclear factor-erythroid 2-related factor 2 (Nrf2). Moreover, it suppressed the activation of OCs through down-regulating the expression of integrin β3, PKC-β, and autopaghy related 5 (43, 44). Besides, dehydrocostus lactone reduced RANKL-induced OC formation and differentiation via modulating NF-κB signaling pathway both in vitro and in vivo (41, 42).

Therefore, costunolide owns the ability to increase bone formation by modulating K_ATP channel and activating PI3K/Akt signaling pathway in OBs, and dehydrocostus lactone can decrease OC differentiation via inhibiting NF-κB signaling pathway.

**Diterpenoids**

_Euphorbia factor L1_ (EFL1) is an active diterpenoid composition extracted from the seed oil of Chinese herb _Euphorbia lathyris_ L. (Qian Jin Zi in Chinese) (106). EFL1 inhibited RANKL-induced osteoclastogenesis by inhibiting c-Fos expression and NF-κB activation. Meanwhile, apoptosis induced by EFL1 in differentiated OCs resulted from caspase activation and enhanced Fas ligand expression. In mice, EFL1 ameliorated bone destruction induced by inflammation and ovariectomy. These findings demonstrated that EFL1 can block OC differentiation through modulating inflammatory responses and trigger Fas-regulated apoptosis, which offers the potential to treat OP caused by excessive Ocs (45).

Abietic acid is a bioactive diterpene isolated from _Pimenta racemosa_ var. _grisosa_ which exhibits anti-obesity and anti-inflammatory activities (107). In RAW264.7 cells and mouse BMMs, abietic acid inhibited RANKL-induced OC formation via suppressing NF-κB and MAPK signaling pathways. It also decreased the expression of osteoclastic genes, such as NFATc1, tartrate-resistant acid phosphatase (TRAP), dendritic cell specific transmembrane protein (DC-STAMP), and c-Fos. In C57BL/6 male mice of LPS-induced OP (52). Furthermore, Zheng et al. found that abietic acid played a dual role via targeting sterol regulatory element-binding protein 2 (SREBP2) and estrogen-related receptor alpha (ERRα) to suppress RANKL-mediated osteoclastogenesis and restrained bone loss induced by ovariectomy (53).

_Crocus sativus_ L., shows various pharmacological activities (116, 117). It was observed that crocin treatment mitigated bone loss in metabolic syndrome-induced OP rat model (118). Meanwhile, this research showed anti-inflammatory and anti-oxidative activities of crocin which significantly decreased the production of IL-6, TNF-α, reduced glutathione (GSH), and superoxide dismutase (SOD). In RAW264.7 cells, crocin attenuated the dysfunction of OCs induced by methylglyoxal via modulating glyoxalase I, oxidative stress, and mitochondrial function (54). Moreover, Fatemeh et al. observed that crocin could effectively improve the differentiation of BMSCs, by inhibiting NF-κB signaling pathway activation, crocin treatment suppressed RANKL-induced bone resorption and OC formation (55, 119).

_Kirenol_ is a bioactive diterpenoid compound derived from _Siegesbeckia orientalis_ L. that was used as an anti-rheumatic TCM (120, 121). Kim et al. demonstrated that kirenol stimulated OB differentiation via activation of BMP and Wnt/β-catenin signaling pathways in MC3T3-E1 cells, which increased the levels of AP, OPN, type I collagen, and OB differentiation markers, as well as the OPG/RANKL ratio (57). Furthermore, kirenol treatment suppressed RANKL-induced OC formation and the NFATc1/Cav-1 signaling pathway in BMMs and OVX rats, consequently preventing ovariectomy-induced OP (56).

Tanshinone IIA is an abietane diterpenoid isolated from _Salvia miltiorrhiza_ Bunge (Danshen) that is used for the...
treatment of trauma and fractures in clinical according to the dispelling stasis theory of TCM (122). 36 clinical trials used Salvia miltiorrhiza to treat different kinds of osteoporosis displayed high efficacy and low toxicity (123). Modern pharmacological studies showed that the ethanol extract of Salvia miltiorrhiza could inhibit trabecular bone loss by restraining bone resorption both in OVX and naturally menopaused mice (124). Tanshinone IIA blocked dexamethasone induced OB apoptosis through the suppression on NADPH oxidase (Nox) 4-derived ROS production. In addition, it blocked RANKL-mediated OC differentiation by decreasing the expression of c-Fos and NFATc1 (60). Tanshinone IIA could attenuate the formation of OCs by depressing the NF-kB, PI3K/Akt, and MAPK signaling pathways in OVX mice model (59). Zhu et al. found that tanshinone IIA administration prevented the harmfulness of pathways in OVX mice model (69). Zue et al. found that depressing the NF-κB, PI3K/Akt, and MAPK signaling pathways in OVX mice model (59). Zhu et al. found that tanshinone IIA administration prevented the harmfulness of oxidative stress and promoted the activity and functions of OBs in genetic OP model, Wnt1<sup>−/−</sup>sw<sup>/sw</sup> mice, through regulating the NF-kB signaling pathway (125). Recently, in streptozotocin (STZ)-induced C57BL/6 diabetic mice, tanshinone IIA treatment restrained the activity of renin that resulted in protecting OP (58). As another abietane diterpenoid constituent obtained from Salvia miltiorrhiza, tanshinone VI significantly suppressed the differentiation of OCs and bone resorption via down-regulating the expression of RANKL and activation of NF-κB (61).

Triptolide, the major active diterpenoid component isolated from Tripterygium wilfordii Hook F, has been used in TCM for hundreds of years to treat cancer and bone loss (126, 127). A recent study suggested that triptolide effectively suppressed the activation of NF-κB induced by RANKL, as well as tumor cell- and RANKL-induced OC formation (63). Triptolide showed the protective effects on bone loss both in old male rats and OVX C57BL/6 mice (62, 64). Triptolide could suppress RANKL-induced OC formation and prevented the bone resorption of OCs in BMSCs and RAW264.7 cells, resulting from inhibiting PI3K/Akt/NFATc1 signaling pathway.

Oridonin is an ent-kaurane diterpenoid extracted from the TCM herb Rabdosia rubescens (Hems.) Hara (128). As a plant metabolite, oridonin acts as an anti-tumor agent, angiogenesis inhibitor, apoptosis inducer, anti-asthmatic agent, and anti-bacterial agent (129, 130). Recent studies demonstrated that oridonin could maintain bone homeostasis (65, 66). In ovariectomy-induced OP mouse model, oridonin could protect bone loss via inhibiting osteoclastogenesis and enhancing osteogenesis by inhibiting interferon-related development regulator 1 (Ifrd1) and 1k_Beta-mediated p65 nuclear translocation. Simultaneously, in vitro study revealed that oridonin motivated osteogenesis by Wnt/β-catenin signaling pathway and suppressed RANKL-induced OC formation in BMSCs.

In conclusion, diterpenoids are mostly investigated terpenoids that exert superior anti-OP efficacy by affecting various signaling pathways. In OBs, andrographolide, kirenol, and oridonin activate Wnt/β-catenin signaling pathway; andrographolide inhibits RANKL/RANK and NF-κB signaling pathways; tanshinone IIA blocks NF-κB signaling pathway. In OCs, euphorbia factor L1, abietic acid, carnosic acid, crocin, tanshinone IIA, and triptolide depress NF-κB signaling pathway; crocin, tanshinone IIA, and triptolide activate PI3K/Akt signaling pathway; andrographolide inhibits RANKL/RANK signaling pathway; abietic acid, carnosic acid, and tanshinone IIA inhibit MAPK signaling pathway; kirenol, tanshinone IIA, and triptolide depress NFATc1 signaling pathway; euphorbia factor L1 and carnosic acid promote Nrf2 signaling pathway.

### Triterpenoids

Lupeol is a major active lupine-type pentacyclic triterpenoid of Sorbus commixta Hedlund and Callastrus orbicularis Thunb (131). Recently, lupeol has attracted the attention of researchers for its osteogenic activity. On one hand, lupeol significantly suppressed OC differentiation and bone resorption mediated by 1α, 25-(OH)<sub>2</sub>D<sub>3</sub> and prostaglandin E2 (PGE2) via inhibiting the activities of MAPK and transcription factors (NF-κB, NFATc1, and c-Fos). On another hand, lupeol decreased hypercalcaemic mediated bone loss in C57BL/6 mice (67). In addition, lupeol in bombax ceiba contributed to relieve bone fragility and fracture (132).

Alisamatis Rhizoma is a famous traditional Chinese herb, which has been used for hepatoprotective, diuretic, hypolipidemic, anti-tumor, anti-inflammatory and anti-diabetic treatments for more than ten centuries (133, 134). More and more researches reported that the terpenoids constituents of this herb, such as the protostane triterpenes compounds Alisol B (69), Alisol A 24-acetate (71, 135), Alisol B 23-acetate (68), and Alisol C 23-acetate (70), own the protective activity against bone loss. Alisol A 24-acetate suppressed OC differentiation mediated by RANKL through downregulating NFATc1 and restraining the DC-STAMP and cathepsin K expression in mouse BMMs (71). Moreover, in OVX mice, alisol A 24-acetate and alisol C 23-acetate could effectively protect bone loss (70, 135). Alisol B suppressed the RANKL-induced osteoclastogenesis in mouse BMMs and stopped bone loss in 2-methylene-19-nor-(20S)-1a,25(OH)<sub>2</sub>D<sub>3</sub> (2MD)-induced hypercalcaemia mouse model (69).

As a member of the pentacyclic triterpenoids, oleanolic acid is a free acid or triterpenoid saponins in many Chinese herbs, such as Nvzhennzi (Ligustri lucidi W. T. Aiton), Baihuasheshcao (Hedyotis diffusa), Renshen (Panax ginseng C. A. Meyer), and Sanqi (Panax Notoginseng (Burk.) F.H.Chen). Nvzhennzi has been clinically applied in the treatment of OP for over 1,000 years (136). Chen et al. summarized more than 150 articles and reviews on the anti-osteoporosis activity of Ligustri lucidi. In TCM, Ligustri lucidi is believed to have anti-osteoporosis effects, improve liver and kidney deficiency and reduce lower back pain. Pharmacological experiments showed Ligustri lucidi improved bone metabolism and bone quality in OVX, growing, aged and diabetic rats via regulating PTH/FGF-23,1α,25-(OH) D3/CaSR, Nox4/ROS/NF-κB, and OPG/RANKL/cathepsin K signaling pathways (137) Oleanolic acid could suppress RANKL-mediated osteoclastogenesis in BMMs, and attenuate bone loss through decreasing the quantity of OC in C57BL/6 OVX mouse model (72). Furthermore, it has been proved that oleanolic acid modulated the ER alpha/miR-503/RANK signaling pathway to inhibit RANKL-induced osteoclastogenesis in...
RAW264.7 cells (138). In aged female rats and mature OVX mice, oleanolic acid regulated vitamin D metabolism to exhibit osteoprotective effect (73). The investigation with high-throughput metabolomics showed that oleanolic acid ameliorated the disordered metabolism state in glucocorticoid-induced OP rats (139). In addition, five oleanolic acid glycosides of *Achyranthes bidentata* also exerted inhibitory effect on the formation of OC-like multinucleated cells (OCLs) induced by 1α, 25-(OH)₂D₃ (140).

Ursolic acid, as the isomer of oleanolic acid, is a ubiquitous active triterpenoids constituent in traditional Chinese medicinal herbs, such as *Salvia miltiorrhiza* (141, 142), *Fructus ligustri lucidi* (143), and *Eriobotrya japonica* (144, 145). Ursolic acid exhibited multiple pharmacological activities, including anticancer, anti-inflammatory, anti-anaphylaxis, and anti-aging (146–148). In recent years, ursolic acid has attracted the attention of researchers for its osteogenic activity. Lee et al. proved that ursolic acid induced the expression of OB-specific genes by activating NF-κB, MAPK, and activator protein-1. Moreover, they demonstrated the osteogenic activity of ursolic acid in a mouse calvarial bone model (74). As the two most abundant ingredients in *Fructus ligustri lucidi*, both ursolic acid and oleanolic acid regulated the expression of bone turnover markers and calcium balance in mature OVX rats. In addition, the combination of these two compounds significantly improved bone properties and vitamin D metabolism in aged female rats (143, 149). Tan et al. observed that ursolic acid prevents OC differentiation induced by RANKL in RAW 264.7 cells through targeting XPO5 (150).

Glycyrrhizic acid, as well as glycyrrhetinic acid, are extracted from the root of *Glycyrrhiza glabra* L., and glycyrrhizic acid is formed by the combination of pentacyclic triterpenoid glycoside and glycyrrhetinic acid (151). Both of them showed protective effects on glucocorticoid-induced OP (152). Glycyrrhizic acid and glycyrrhetinic acid could act as the ligands for glucocorticoid receptor (GR), which further modulated glucocorticoid resistance and ameliorated inflammatory responses by disrupting the GR-heath shock protein 90 (HSP90) (76, 153). Glycyrrhizic acid prevented glucocorticoid-induced OP in male SD rats through inhibiting the 11β-hydroxysteroid dehydrogenase type 1 enzyme (11β-HSD1) (75). Furthermore, Yamada et al. found that in an aging mouse model of periprosthetic osteolysis, glycyrrhizic acid alleviated inflammatory bone loss and increased senescence-protective sirtuins expression (77). In OVX mice model, glycyrrhizic acid treatment improved bone metabolism and suppressed OC differentiation via modulating NF-κB, ERK, and JNK signaling pathways (7, 154). Glycyrrhetinic acid inhibited osteoclastogenesis via decreasing RANKL-mediated association of RANK and TNF receptor associated factor 6 (TRAF6), and consequently inactivating the NF-κB and MAPK signaling pathways in *vitro* (BMMs and RAW264.7 cells) and *in vivo* (OVX C57BL/6 mice) (78).

Betulinic acid is a pentacyclic lupane-type triterpene derivative of *Betula pubescens* Ehrh., exhibiting multiple biological effects including osteogenic activity. Betulinic acid could enhance the proliferation, differentiation, and mineralization of osteoblastic MC3T3-E1 through regulating the BMP/Smad/Runx2 and β-catenin signal pathways (81). Furthermore, betulinic acid reduced RANKL-associated osteoclastogenesis via suppressing the MAPK and NFATc1 signaling pathways in BMMs isolated from C57BL/6 mice. In the osteoporotic C57/BL6 mice, betulinic acid prevented ovariectomy-induced bone loss (80).

Ginsenoside Rg1, a tetracyclic triterpenoid, is an active compound in *Panax ginseng* C. A. Meyer and *Panax japonicus* (T. Nees) C. A. Meyer, which acts as a neuroprotective agent and pro-angiogenic agent. Ginsenoside Rg1 promoted the proliferation and odontogenic/osteogenic differentiation of human dental pulp stem cells (hDPSCs), stimulated the proliferation of BMSCs, and suppressed the maturation and differentiation of OCs (79). Zishen Jiangtang Pill (ZIP) is a formula of Chinese medicine, which regulated bone metabolism in diabetic OP (DOP) and consequently exhibited a protective effect. As the primary active ingredient of ZIP, Ginsenoside Rg1 improved the ultrastructure and histomorphology of bone and islets in DOP rats (155).

Limonen is a tetracyclic triterpenoid of various TCM and fruits, such as *Evodia rutaecarpa*, *Coptidis rhizoma*, *Cortex chinensis phellodendri*, *bergamot*, *Aurantii fructus immaturus*, *Citri reticulatae pericarpium*, and citrus fruits (156). Early study showed that limonen significantly inhibited bone resorption and reduced the number of multinucleated cells with TRAP-positive nature in OC-like cell model (82). Otherwise, limonen treatment modulated the ERK and p38-MAPK signaling in osteoblast MC3T3-E1 cell line to induce osteogenic differentiation (83).

Nomilin, a furan-containing triterpenoid isolated from medicinal citrus, showed inhibitory effects on RANKL-stimulated OC differentiation and bone resorption in RAW 264.7 cells and mouse BMMs cells, resulting from the inhibition of-NFATc1 and MAPK signaling pathways (84).

Diosgenin and dioscin are steroid sapogenin triterpenoids, which are extracted from *Dioscorea nipponica* Makino (157). It was reported that diosgenin could suppress osteoclastogenesis and bone resorption. Meanwhile, it enhanced the osteogenic activity of OBs that contributed to increased bone formation in *vitro*, and anti-osteoporotic effect in vivo (85, 158–162). Diosgenin ameliorated bone loss by decreasing the RANKL/OPG ratio in OVX rats (85, 163) and retinoic acid-induced OP rats (164). Similarly, dioscin enhanced osteoblastogenesis and inhibited osteoclastogenesis to prevent ovariectomy-induced bone loss (165). In addition, dioscin blocked OC differentiation and bone resorption via inhibiting the activation of Akt signaling pathway (86). In human and mouse OB-like cell lines, dioscin promoted the proliferation and differentiation of OBs via Lrp5 and ER pathway (87).

Ophiopogonin D is a saposins triterpenoid extracted from the TCM *Ophiopogon japonicus* (L. f.) Ker-Gawl. and has been applied in clinical use for a long time. Ophiopogonin D suppressed ROS generation to exert anti-OP effects via the FoxO3a/β-catenin signaling pathway in both RAW264.7 and MC3T3-E1 cells. In RAW264.7 cells, ophiopogonin D decreased the expression of Osteoclastic genes and the activity of CTX1 and
TRAP, which are bone degradation markers in serum. In MC3T3-E1 cells, ophiopogonin D significantly promoted cell proliferation and increased the gene levels of some osteogenic markers (88). Furthermore, Yang et al. highlighted that ophiopogonin D owned the ability to inhibit Krüppel-like factor 3 (KLF3), resulting in increased abundance of vessels in the bone tissue for bone formation (89).

As a pentacyclic triterpenoid compound, cycloastragenol is the aglycone derivative of astragaloside IV isolated from the root of *Astragalus membranaceus* (Fisch.) Bunge, which is a TCM used for thousands of years (166). Recent study reported that cycloastragenol might be a candidate drug to treat glucocorticoid-induced OP (GIOP) through alleviating the inhibition of osteogenic differentiation induced by dexamethasone (90). Yu et al. also observed that cycloastragenol treatment could improve bone formation, protect bone microstructure from degradation, reduce OC number, and augment bone biomechanical properties in both bone loss models induced by aging and D-galactose. Furthermore, cycloastragenol promoted the differentiation, viability, and mineralization of osteoblastic MC3T3-E1 cells. Cycloastragenol could also alleviate bone loss through increasing osteoactivin expression (167).

Hederagenin is a pentacyclic triterpenoid sapogenin extracted from *Hedera helix* (common ivy). In BMM cell model, hederagenin depressed the formation and bone (hydroxyapatite) resorption of OC induced by RANKL. Mechanism study revealed that hederagenin reduced the production of intracellular reactive oxygen species (ROS) and the activation of MAPK signaling pathway (ERK and p38), causing decreased induction of c-Fos and NFATc1. Similar to the *in vitro* effects, hederagenin treatment significantly prevented bone loss in OVX mice *via* inhibiting RANKL-induced bone resorption and OC generation (91). Meanwhile, hederagenin 3-O-((2-O-acetyl)-α-L-arabinopyranoside remarkably elevated the protein levels of BSP and osteocalcin and augmented AP activity (168).

Tubeimoside I, isolated from the Chinese medicinal herb *Bolbostemma paniculatum* (Maxim) Franquet (Cucurbitaceae), is a natural pentacyclic triterpenoid, and traditionally used for the treatment of snake venoms and inflammation. Recently, it was reported that tubeimoside I could inhibit the formation and function of OCs, as well as type 2 diabetes-induced decrease of bone mass in SD rats, resulting from down-regulating IkBα degradation which subsequently suppressed NF-κB transcriptional activity (92).

In summary, triterpenoids are potential anti-OP candidates with multi-target characteristics. In OBs, betulinic acid can activate Wnt/β-catenin signaling pathway; ophiopogonin D stimulates FoxO3a/β-catenin signaling pathway; ursolic acid, limonin, diosgenin, and dioicin promote MAPK signaling pathway. In OCs, diosgenin and dioicin enhance PI3K/Akt signaling pathway; lupeol, glycyrrhetinic, and tubeimoside I inhibit NF-κB signaling pathway; oleanolic acid inhibits RANKL/RANK signaling pathway; lupeol, betulinic acid, nomilin, and hederagenin depress MAPK signaling pathway; lupeol, alisol B, betulinic acid, and nomilin block NFATc1 signaling pathway.

**CONCLUSION AND PROSPECTS**

TCM has been widely used around the world for thousands of years to treat various diseases. These *in vivo* and *in vitro* findings discussed above demonstrate that terpenoids in natural Chinese medicine own the potential ability to provide therapeutic benefits for OP treatment.

Although terpenoids are beneficial for OP treatment, some terpenoids have been reported to be toxic. Cantharidin, a monoterpene obtained from *Mylabris phalerata* showed nephrotoxicity by suppressing the lactate dehydrogenase expression and intracellular release (169). Diterpene compound Pekinin C and pekineval also exhibited serious cytotoxicity intestinal toxicity (170). Thus, modification of their structures for lower toxicity and stronger efficacy are needed. For example, the quinoxaline derivative of oleanolic acid, QOA-8a, could not only inhibit bone resorption but also stimulate bone formation, playing dual roles in anti-OP (171). Meanwhile, the addition of quinoxaline contributed to lower cytotoxicity (172). Comparing with andrographolide itself, its derivative 14-deoxy-11,12-didehydroandrographolide showed stronger anti-osteoclastogenesis effect with significantly reduced cytotoxicity (173, 174). Therefore, structure modification will be an optional strategy for anti-OP drug development based on natural terpenoids. In addition, other problems, such as poor water solubility, short half-life, poor stability, and low bioavailability, severely limit the development and clinical use of TCM. The application of modern technologies (nanotechnology and co-crystallization) can overcome these short comings (175–177). Hence, for those terpenoids with perfect anti-OP efficacy but poor water solubility, we can apply nanoparticles in the drug delivery.

Nowadays, though a massive of studies reveal the anti-OP effects and molecular mechanisms of terpenoids, most of their direct targets as well as regulation mechanisms have not been illustrated. Several advanced technologies, such as proteomics (178) and systems pharmacology-based approaches (179, 180), have offered effective tools to identify potential targets of natural terpenoids. Proteomics and systems pharmacology-based approaches could perform the large-scale study of proteins and the major targets of most compounds. On the one hand, it is helpful to explain the exact pharmacological mechanism for preclinical drug development. On the other hand, the screening of terpenoids targeted proteins in OP treatment benefits researchers for understanding the pathogenesis of osteoporosis.

Moreover, TCM not only exerted anti-OP functions alone through diverse signaling pathways, but also showed enhancing effects *via* combining with clinically used hormones (estrogen or growth hormone) to prevent bone loss (181). This combination can avoid possible toxic side-effects and improve clinical efficacy (182). In the future, more in-depth and high-quality clinical researches are essential to ensure the safety, efficacy, and
specificity of the terpenoids, which will provide more evidence for the candidates in efficiently anti-osteoporotic applications.

AUTHOR CONTRIBUTIONS

JF and YZ: conceptualization. YZ and ML: writing — original draft preparation. QI, HK, QL, and L-FZ: editing, and revising. JF: supervision. All authors contributed to the article and approved the submitted version.

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FUNDING

The work was supported by the National Natural Science Foundation of China (No.82074278), the Guangdong Basic and Applied Basic Research Foundation (No. 2021A1515110584), Special Foundation of Guangdong Educational Committee (No. 2021ZDZX2001), and Guangdong Province Science and Technology Plan International Cooperation Project (No. 2020A050510052).
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