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Roles of plant-derived natural compounds in the prevention and treatment of osteoporosis

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Abstract

Osteoporosis is a systemic disease, and epidemiological projections indicate that by 2050, approximately 23.43% of the Chinese population over 50 years of age will be affected. Given the poor prognosis associated with osteoporosis, the exploration of safe and effective natural products is of considerable significance. Studies investigating the chemical constituents of traditional Chinese medicine in cellular and/or animal models have demonstrated bone-protective effects. Although most of these compounds lack clinical data, they hold considerable potential as lead candidates for drug development. In-depth study of the structure–activity relationship of these natural products not only contributes to elucidating the mechanisms of action but also provides a theoretical basis for the development of novel antiosteoporosis therapies. This review summarizes natural products with potential antiosteoporotic effects reported between 2020 and 2024. Overall, plant-derived natural compounds exhibit antiosteoporotic effects by regulating bone remodeling, inflammation, and oxidative stress, highlighting their promise as multitarget therapeutic candidates.

Key words: Flavonoids; Natural products; Osteoporosis; Saponins; Terpenoids

1. Introduction

Osteoporosis, characterized by low bone mineral density (BMD), is a skeletal disorder manifested by reduced bone mass, deteriorated bone microarchitecture, impaired skeletal structure, and decreased bone strength, leading to an increased risk of fractures.[1] The onset of osteoporosis is influenced by various factors, including genetic predisposition, gender, age, vitamin D levels, nutritional status, lifestyle choices (e.g., physical inactivity, smoking, and excessive alcohol consumption), as well as chronic diseases and certain medications. The pathological mechanism of osteoporosis primarily arises from an imbalance between osteoblast and osteoclast activity during bone remodeling. The Wnt signaling pathway plays a crucial role in regulating the differentiation and proliferation of osteoclasts and osteoblasts.[2] Additionally, key inflammatory factors such as interleukin (IL)-1 and tumor necrosis factor-alpha (TNF-α) synergistically enhance osteoclast formation through the TNF receptor-associated factor 6 and nuclear factor-kappa B (NF-κB) pathways. Fibroblast growth factors regulate osteoblast proliferation, differentiation, and bone formation by activating pathways such as fibroblast growth factor receptors (FGFR) and mitogen-activated protein kinase (MAPK), thereby regulating the expression of runt-related transcription factor 2 (Runx2), alkaline phosphatase (ALP), osteopontin, and osteocalcin (OCN). Abnormal activation of these signaling pathways collectively promotes the onset and progression of osteoporosis.[3]

Several drugs have been developed for the treatment of osteoporosis. Commonly used options include bisphosphonates, hormone therapy, calcitonin, selective estrogen receptor (ER) modulators, and strontium ranelate, all of which are effective treatments.[4] However, these treatments are often associated with side effects, including oily skin, fluid retention, nausea, long-term toxicity, and, in men, an increased risk of prostate cancer.[5] Therefore, there is an urgent need for novel, natural therapies with fewer side effects to provide safer and more effective management of osteoporosis.

Natural compounds, especially plant extracts, have received increasing attention due to their potential skeletal-protective effects and favorable safety profiles. This review aims to summarize the structure and function of natural products with potential antiosteoporotic activity reported between 2020 and 2024, integrating information on their molecular targets and signaling pathways involved in osteoporosis. We discuss various natural compounds that have shown potential against osteoporosis, including flavonoids, terpenoids, saponins, alkaloids, and polysaccharides.

2. Literature search strategy

We conducted a comprehensive search of PubMed using keywords such as "flavonoids and osteoporosis," "terpenoids and osteoporosis," "saponins and osteoporosis," "alkaloids and osteoporosis," and "polysaccharides and osteoporosis." The search was restricted to English-language articles and sorted by publication year. A total of 50 articles and reviews published between 2020 and 2024 were included in this analysis.

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3. Natural plants and compounds

3.1. Flavonoids

3.1.1. Apigenin

Apigenin (Supplemental Fig. S1, https://links.lww.com/STCM/A74) is a natural flavonoid found in chamomile and celery. Apigenin has been shown to significantly enhance the osteogenic differentiation of mesenchymal stem cells and accelerate fracture healing *in vivo*. This effect is mediated through activation of the Wnt/β-catenin signaling pathway, leading to increased expression of osteogenic genes such as Runx2, ALP, and collagen type I alpha 1 (COL1A1).[6] Furthermore, apigenin can alleviate the senescent phenotype of bone marrow mesenchymal stem cells (BMSCs) by reducing reactive oxygen species and downregulating senescence-associated molecules, including P53, P21, and P16, as well as inflammatory factors IL-6 and TNF-α. This activity helps maintain stem cell viability and differentiation potential, thereby delaying bone loss.[7]

3.1.2. Luteolin

Luteolin (Supplemental Fig. S1, https://links.lww.com/STCM/A74), a natural flavonoid, is present in pepper, mint, and chamomile. Luteolin could improve mitochondrial dysfunction, alleviate gasdermin E-mediated pyroptosis, and maintain osteogenesis via activating the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) axis, offering a new therapeutic strategy for postmenopausal osteoporosis.[8] Luteolin also significantly mitigates dexamethasone-induced osteoporosis by promoting autophagy via the miR-125b-5p/sirtuin 3 (SIRT3)/AMP-activated protein kinase (AMPK)/mammalian target of rapamycin (mTOR) axis. Consistently, in animal experiments, luteolin improves bone histomorphometry, inhibits miR-125b-5p and mTOR expression, and upregulates SIRT3 and AMPK.[9]

3.1.3. Scutellarein

Scutellarein (Supplemental Fig. S1, https://links.lww.com/STCM/A74) is a flavonoid found in *Scutellaria baicalensis*. Scutellarein has been shown to significantly alleviate osteoarthritis progression by inhibiting the PI3K/Akt/NF-κB pathway. *In vitro*, it reduces the expression of pro-inflammatory factors and cartilage-degrading enzymes in IL-1β-induced chondrocytes, while significantly upregulating cartilage matrix components and transcription factors. In mouse models of osteoarthritis, scutellarein alleviates cartilage damage and improves joint function.[10]

3.1.4. Chrysin

Chrysin (Supplemental Fig. S1, https://links.lww.com/STCM/A74) is a dietary flavonoid found in various plant sources, such as blue passionflower and honey. In a mouse model of bone lysis induced by titanium particles, chrysin was shown to significantly inhibit osteoclast formation and bone resorption. This effect is primarily mediated through suppression of the NF-κB and MAPK (extracellular signal-regulated kinase [ERK], c-Jun N-terminal kinase [JNK]) signaling pathways, downregulating nuclear factor of activated T-cells cytoplasmic 1 (NFATc1), cellular Fos (c-Fos), and other osteoclast-related genes, thereby delaying bone destruction.[11]

3.1.5. Quercetin

Quercetin (Supplemental Fig. S1, https://links.lww.com/STCM/A74) and its derivatives are naturally occurring and found in the stem bark, flowers, leaves, buds, seeds, and fruits of many plants. *In vitro*, quercetin stimulates the expression of osteoblast markers such as bone morphogenetic protein (BMP), Runx2, OCN, osteonectin, and type I collagen in mouse adipose-derived stem cells. In the MAPK signaling network, which comprises ERK, JNK, and p38 pathways, quercetin activates ERK and p38 signaling but not JNK.[12]

3.1.6. Rutin

Rutin (Supplemental Fig. S1, https://links.lww.com/STCM/A74) is a flavonoid glycoside, also known as vitamin P. It is a flavonoid compound extracted from plants, found in *Ruta graveolens*, bitter buckwheat, and buckwheat seed coats. In ovariectomized (OVX) mouse models, rutin can significantly improve bone histomorphometric parameters and reduce serum levels of ALP, IL-1β, IL-6, and TNF-α, indicating its antiosteoporotic effect through inhibition of osteoclast activity and inflammatory factor expression.[13] Furthermore, using layer-by-layer assembly technology to prepare rutin coatings on titanium implant surfaces markedly enhances bone formation in osteoporotic rat models by activating osteoblast-related signaling pathways such as Wnt/β-catenin, thereby improving osteoblast differentiation and mineralization.[14]

3.1.7. Kaempferol

Kaempferol (Supplemental Fig. S1, https://links.lww.com/STCM/A74) is an important flavonoid widely distributed in the rhizomes or fruits of various plant species. Kaempferol promotes the differentiation of BMSCs into osteoblasts by regulating the SOX2/miR-124-3p/PI3K/Akt/mTOR axis. Upregulation of SRY-box transcription factor 2 (SOX2) inhibits miR-124-3p expression, which in turn activates the PI3K/Akt/mTOR pathway, promoting the expression of osteoblast-related genes such as Runx2 and ALP and enhancing bone formation.[15]

3.1.8. Myricetin

Myricetin (Supplemental Fig. S1, https://links.lww.com/STCM/A74) is a flavonol compound extracted from the bark of *Myrica rubra* plant. *In vitro* studies have shown that myricetin 3-*O*-β-D-galactoside, a derivative of myricetin, promotes osteogenic differentiation of human BMSCs (hBMSCs), while inhibiting their adipogenic differentiation. This effect is mediated through activation of the Wnt/β-catenin and BMP pathways and inhibition of the peroxisome proliferator-activated receptor gamma (PPARγ) pathway, resulting in upregulation of osteogenic genes such as Runx2 and ALP, and downregulation of adipogenic genes such as PPARγ and sterol regulatory element-binding protein 1c (SREBP1c).[16]

3.1.9. Icariin

Epimedii folium, a traditional herbal medicine, contains icariin (Supplemental Fig. S1, https://links.lww.com/STCM/A74) and epimedin II as its major active components. *In vitro* studies have shown that icariin can modulate the receptor activator of nuclear factor-κB ligand (RANKL) signaling pathway by activating ER alpha and inhibiting cellular src kinase phosphorylation, thereby suppressing RANKL-induced differentiation of RAW264.7 cells into osteoclasts and reducing the expression of osteoclast-related genes (e.g., tartrate-resistant acid phosphatase [TRAP] and cathepsin K [CTSK]).[17]

3.1.10. Puerarin

Puerarin (Supplemental Fig. S1, https://links.lww.com/STCM/A74) is the primary active component extracted from the roots of *Pueraria lobata*. Puerarin prevents bone loss in OVX rats by suppressing osteoclast activation and bone resorption through suppression of the integrin-β3-proline-rich tyrosine kinase 2 (Pyk2)/Casitas B-lineage lymphoma (Cbl)/proto-oncogene

tyrosine-protein kinase (Src) signaling pathway, without affecting osteoclast formation or apoptosis.[18] Moreover, the activation of ERK1/2 and p38 MAPK signaling pathways contributes to puerarin-mediated osteogenesis, with ERK1/2 playing a more prominent role than p38 in driving the osteogenic phenotypic differentiation of BMSCs.[12]

3.1.11. Soy isoflavones

The 3 major glycosides that define soybean isoflavones (Supplemental Fig. S1, https://links.lww.com/STCM/A74) are daidzein, genistein, and glycitein. Isoflavones derived from chickpea sprouts have been reported to dual-regulate bone remodeling by promoting osteogenic differentiation through the ER/osteoprotegerin (OPG)/RANKL pathway and inhibiting osteoclastic bone resorption via NF-κB inhibition, thereby improving osteoporosis in OVX rats.[19] Equol, a metabolite of soy isoflavones, selectively binds to ERβ, upregulates OPG expression, and increases the OPG/RANKL ratio in osteoblasts. *In vivo* studies further demonstrate that equol ameliorates femoral microarchitecture and enhances BMD in postmenopausal osteoporosis rat models.[20]

3.1.12. Genistein

Genistein (Supplemental Fig. S1, https://links.lww.com/STCM/A74) is considered a soy isoflavone with anticancer properties, primarily found in leguminous plants. In the present study, we found that genistein inhibited bone loss, downregulated sequestosome 1 (P62/SQSTM1) levels, and rebalanced the dysregulated osteoblast-adipocyte differentiation of MSCs in the femurs and tibias of OVX rats. *In vitro*, genistein-induced autophagy activated the Wnt/β-catenin signaling pathway by promoting adenomatous polyposis coli degradation, resulting in osteoblastic differentiation of OVX-MSCs.[21]

Chondroitin sulfate (CS) is a type of glycosaminoglycan widely distributed in human and animal tissues, such as cartilage, periosteum, and tendons. Low molecular weight CS exhibits enhanced biological activities, including antioxidant, anticoagulant, and immunoregulatory effects.[22] In a glucocorticoid-induced osteoporosis model, an enzymatically prepared chitosan–CS–genistein nanocomplex markedly improved BMD, bone microstructure, and bone strength. CS and genistein synergistically promoted osteoblast differentiation, inhibited osteoclast activity, and regulated oxidative stress and inflammatory responses, thereby restoring bone metabolic balance.[23]

3.1.13. Naringin

Naringin (Supplemental Fig. S1, https://links.lww.com/STCM/A74) is primarily found in grapefruit and other citrus fruits. Naringin protects bone structure and increases BMD by activating osteogenic signaling pathways such as Wnt/β-catenin and BMP/Smad, upregulating osteogenesis-related genes, and downregulating the RANKL/OPG axis to inhibit osteoclast formation. In addition, it suppresses oxidative stress and inflammatory responses, further mitigating bone loss.[24]

3.1.14. Epigallocatechin gallate (EGCG)

EGCG (Supplemental Fig. S1, https://links.lww.com/STCM/A74) is a major catechin found in green tea. As an antioxidant, EGCG can directly bind to receptor activator of nuclear factor κB (RANK) and RANKL, disrupting their interaction and suppressing RANKL-induced activation of NF-κB and MAPK signaling pathways. This inhibition reduces the expression of key downstream regulators such as NFATc1, c-Fos, and TRAP in osteoclast precursors, ultimately inhibiting osteoclastogenesis.[25] We summarized the signaling pathways and associated functions of flavonoids in combating osteoporosis in Supplemental Table S1, https://links.lww.com/STCM/A75.

3.2. Terpenoids

Terpenoid alkaloids represent a relatively small but biologically significant group of compounds, primarily derived from plants, with a few sourced from animals and microorganisms (Supplemental Table S2, https://links.lww.com/STCM/A75). Based on their structural skeletons, they can be classified into monoterpenoids, sesquiterpenoids, diterpenoids, triterpenoids, and tetraterpenes (Fig. 1).[26]

3.2.1. Limonene

Limonene (Supplemental Fig. S1, https://links.lww.com/STCM/A74) is a natural monoterpenoid compound abundantly found in citrus plants. Limonene promotes osteoblast differentiation and bone nodule formation *in vitro* while inhibiting RANKL-induced osteoclastogenesis and bone resorption (Fig. 1). It decreases pro-resorptive signals from osteoblasts, increases osteoblast differentiation markers such as ALP, Osterix, and Runx2 (Fig. 1), and significantly reduces the expression of pro-inflammatory cytokines such as parathyroid hormone-related protein (PTHrP), IL-1β, and TNF-α.[27]

3.2.2. Andrographolide

Andrographolide (Supplemental Fig. S1, https://links.lww.com/STCM/A74) is a diterpenoid compound derived from the traditional Chinese medicine (TCM) *Andrographis paniculata*. Andrographolide promotes the differentiation of MC3T3-E1 osteoblast precursors and enhances ALP activity, as well as collagen and OCN synthesis *in vitro*. Mechanistically, it upregulates OPG and downregulates RANKL expression. In OVX rat models, andrographolide significantly delays bone loss by inhibiting bone resorption, improving BMD, and preserving trabecular bone structure integrity.[28] Additionally, andrographolide derivatives inhibit osteoclastogenesis by suppressing RANKL-induced NF-κB activation and downregulating the expression of c-Fos, NFATc1, carbonic anhydrase II (CAII), calcitonin receptor (CTR), matrix metalloproteinase-9 (MMP-9), and TRAP, effectively ameliorating bone loss in OVX mice (Fig. 1).[29]

3.2.3. Tanshinone

Tanshinones (Supplemental Fig. S1, https://links.lww.com/STCM/A74), particularly tanshinone II_A, are lipophilic diterpene quinone compounds extracted from *Salvia miltiorrhiza*. Tanshinone II_A downregulates ANG II protein expression in HEK-293 cells expressing human renin. In diabetic mice, treatment with tanshinone II_A significantly increased trabecular BMD, improved trabecular microarchitecture, and expanded trabecular bone area, effectively mitigating osteoporosis.[30] Various tanshinone derivatives, including tanshinone II_A, tanshinone I, tanshinone VI, cryptotanshinone, and 15,16-dihydrotanshinone, positively influence bone turnover. They promote osteoblast differentiation and proliferation by upregulating Runx2 through multiple signaling pathways, such as Wnt, BMP, PI3K/Akt, and ERK1/2, while inhibiting osteoclast formation via suppression of RANKL and NF-κB signaling (Fig. 1).[31]

3.2.4. Forskolin

Forskolin (Supplemental Fig. S1, https://links.lww.com/STCM/A74) is a labdane diterpene derived from the soft wood of the root of *Coleus forskohlii*. Transglutaminase 2 serves as the primary cellular target of forskolin; their interaction induces an

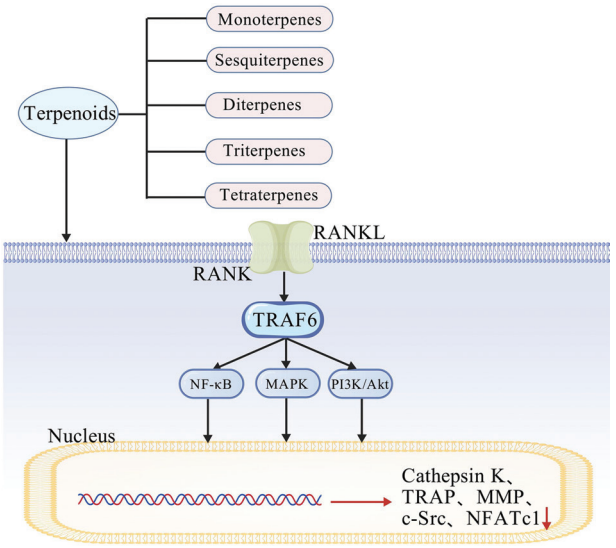

Figure 1. Classification and mechanisms of action of terpenoids. Created with BioGDP.com.

"open" conformation of the enzyme, which enhances mitochondrial dynamics and ATP production, thereby promoting osteoblast differentiation and effectively alleviating osteoporosis in OVX mouse models.[32]

3.2.5. Ursolic acid

Ursolic acid (Supplemental Fig. S1, https://links.lww.com/STCM/A74) is a natural pentacyclic triterpenoid widely distributed in fruits, spices, and medicinal plants. Ursolic acid effectively prevents OVX-induced osteoporosis in rats by improving trabecular microstructure and inhibiting the expression of osteoclast-related factors such as c-Fos and NFATc1. Additionally, it alleviates OVX-induced kidney damage by reducing urea nitrogen and creatinine levels. Importantly, ursolic acid can block the autophagy pathway during osteoclast differentiation, further contributing to its bone-protective effects.[33] Ursolic acid also inhibits RANKL-induced osteoclast differentiation and activity, reducing bone resorption while downregulating osteoclast-related genes such as CTSK and TRAP, thereby maintaining bone mass (Fig. 1). Notably, combining ursolic acid with risedronate sodium in a dissolvable microneedle patch, with the aid of nanocarriers, enhances both bioavailability and targeting, producing synergistic effects that further improve antiosteoporotic efficacy.[34]

3.3. Saponins

3.3.1. Ginsenoside

Ginseng is a well-known herbal medicine. Recent studies have highlighted the osteogenic potential of specific ginsenosides. Ginsenoside Rg_1 (Supplemental Fig. S2, https://links.lww.com/STCM/A74) promotes osteoblast differentiation and mineralization by activating the G protein-coupled estrogen receptor, which subsequently triggers the PI3K/Akt signaling pathway. In a glucocorticoid-induced osteoporotic zebrafish model, ginsenoside Rg_1 significantly upregulated the expression of bone formation-related genes such as Runx2, ALP, and OCN.[35] Ginsenoside Rb_2 (Supplemental Fig. S2, https://links.lww.com/STCM/A74) attenuates osteoclast-specific mRNA and protein expression, including NFATc1, c-Fos, and CTSK, by regulating the NF-κB and MAPK signaling pathways. *In vivo*, ginsenoside Rb_2 protects against bone loss and preserves trabecular bone structure in orchidectomized mice through inhibition of these pathways.[36]

3.3.2. Astragaloside IV (AS-IV)

AS-IV (Supplemental Fig. S2, https://links.lww.com/STCM/A74) is a major active component extracted from the traditional Chinese medicinal herb *Astragalus membranaceus*. AS-IV alleviates D-galactose-induced bone loss and macrophage senescence by regulating the stimulator of interferon genes (STING)/NF-κB signaling pathway, promoting the osteogenic differentiation of BMSCs, and improving bone microstructure and quality in D-galactose-induced senile osteoporosis mice, thereby exerting significant antiosteoporotic effects.[37] However, the poor water solubility and low oral bioavailability of AS-IV limit its application. To overcome challenges, a study developed a methoxy polyethylene glycol-poly(lactic-co-glycolic acid) (mPEG-PLGA) nanoparticle delivery system modified with alendronate, which significantly enhanced the bone-targeting capability and bioavailability of AS-IV. In the OVX osteoporotic mouse model, this nanodelivery system effectively improved bone metabolism markers, restored trabecular architecture, and demonstrated potent antiosteoporotic efficacy.[38]

3.3.3. Panax notoginseng saponin (PNS)

Notoginseng is an important medicinal material in TCM, with its primary active components being PNS. Ginsenoside Rg_3, a saponin extracted from ginseng, inhibits RANKL-induced osteoclast differentiation and formation in RAW264.7 cells by knocking down karyopherin alpha 2 (KPNA2), thereby downregulating TRAP and NFATc1 via the NF-κB signaling pathway. This suggests that KPNA2 may serve as a potential therapeutic target for osteoporosis and the regulation of osteoclast differentiation.[39] In an OVX-induced fracture rat model, PNS regulated the PI3K/Akt/mTOR signaling pathway by activating PI3K, promoting Akt phosphorylation, and subsequently activating mTOR. This cascade enhances vascular endothelial cell function, stimulates osteoblast proliferation, inhibits osteoclast activity, and restores bone metabolic balance.[40] The roles of saponins in osteoporosis are summarized in Supplemental Table S3, https://links.lww.com/STCM/A75.

3.4. Polysaccharides

Polysaccharides are important biomacromolecules present in various organisms, including plants, marine organisms, fungi, bacteria, and animals. Natural polysaccharides have attracted increasing attention due to their various pharmacological activities, such as anti-inflammatory, antioxidant, antitumor, antibacterial, antiobesity, antiviral, anticoagulant, and immunoregulatory properties (Supplemental Table S4, https://links.lww.com/STCM/A75).[41]

3.4.1. Astragalus polysaccharides (APS)

A. membranaceus is a Chinese medicinal herb with a long history of clinical application. APS (Supplemental Fig. S2, https://links.lww.com/STCM/A74) enhances the osteogenic differentiation of hBMSCs by inhibiting miR-760 expression and upregulating ankyrin repeat and FYVE domain containing 1 (ANKFY1). APS stimulates the differentiation and proliferation of hBMSCs by increasing cell viability, elevating the expression of cyclin D1, ALP, OCN, and Runx2, and inducing osteoblast mineralization, thereby exerting antiosteoporotic effects.[42] In

a dexamethasone-induced osteoporosis rat model, APS treatment restored BMD and repaired bone microstructural damage. Additionally, APS significantly reduced acid phosphatase 5, tartrate resistant (ACP5) levels and pro-inflammatory cytokines (TNF-α and IL-2), suggesting that APS ameliorates osteoporosis by suppressing osteoclastogenesis and inflammation.[43]

3.4.2. Fucoidan

Fucoidan (Supplemental Fig. S2, https://links.lww.com/STCM/A74) is a natural polysaccharide derived from brown seaweed. Pectinex-treated fucoidan significantly inhibits RANKL-induced osteoclast differentiation *in vitro*, as evidenced by decreased TRAP activity and downregulation of key osteoclast-related transcription factors, including NFATc1, TRAP, RANK, Src, c-Fos, and microphthalmia-associated transcription factor (Mitf).[44]

3.4.3. Alginate

Alginate (Supplemental Fig. S2, https://links.lww.com/STCM/A74) is a natural acidic polysaccharide extracted from marine brown algae. We developed a functional alginate calcium hydrogel modified with zoledronic acid. This hydrogel promotes osteoblast differentiation and bone formation by activating the Wnt/β-catenin signaling pathway, significantly upregulating the expression of β-catenin, Axin2, OCN, and Sp7 transcription factor (SP7), demonstrating its potential in osteoporosis treatment.[45]

3.5. Alkaloids

Alkaloids are a class of nitrogen-containing natural organic compounds, commonly occurring as secondary metabolites in plants and distributed in roots, leaves, seeds, and other plant parts (Supplemental Table S5, https://links.lww.com/STCM/A75).

3.5.1. Berberine

Berberine (Supplemental Fig. S2, https://links.lww.com/STCM/A74) is a quaternary ammonium isoquinoline alkaloid, mainly found in plants of the Berberidaceae, Cornaceae, and Rutaceae families. It has been shown to delay the progression of osteoporosis, osteoarthritis, and rheumatoid arthritis by modulating multiple signaling pathways and exhibits antiapoptotic, anti-inflammatory, and immunosuppressive activities.[46] A recent study developed a nano-agonist formed through the self-assembly of berberine and chlorogenic acid. The weight ratio of chlorogenic acid to berberine in the nano-agonist can be precisely controlled to ensure consistency, while effectively activating Wnt signaling, regulating osteogenic differentiation, and improving bone loss in OVX-induced osteoporotic mice.[47]

3.5.2. Matrine

Matrine (Supplemental Fig. S2, https://links.lww.com/STCM/A74) is a naturally occurring quinolizidine alkaloid, with the primary botanical source being *Sophora flavescens* Aiton. Oxymatrine (OMT), a quinolizidine alkaloid derived from *S. flavescens,* ameliorates diabetic osteoporosis by altering gut microbiota, decreasing lipopolysaccharide release, and promoting osteoblast proliferation and differentiation via the miR-539-5p/OGN/Runx2 signaling pathway.[48] Moreover, OMT displays potent anti-inflammatory and antioxidant activities. In orchidectomized rats, both testosterone and OMT mitigated osteoporosis, accompanied by reduced inflammatory cytokines (TNF-α and IL-6), reduced malondialdehyde (MDA) and Keap1 levels, increased glutathione (GSH), and upregulated nuclear factor erythroid 2-related factor 2 (Nrf2)/heme oxygenase-1 (HO-1).[49]

3.5.3. Cytisine

Cytisine (Supplemental Fig. S2, https://links.lww.com/STCM/A74) is a naturally occurring bioactive compound classified as an alkaloid, primarily isolated from leguminous plants. Mechanistically, cytisine suppresses RANKL-induced osteoclastogenesis by inhibiting the phosphorylation of JNK/ERK/p38-MAPK, inhibitor of nuclear factor kappa B alpha (IκBα)/p65-NF-κB, and PI3K/Akt signaling pathways, thereby significantly downregulating osteoclast-related genes such as NFATc1, CTSK, MMP-9, and TRAP.[50]

4. Conclusions

TCM formulations are abundant in diverse natural bioactive compounds and exhibit a broad range of pharmacological activities across various disease contexts. Clinical trials and *in vitro* studies have demonstrated that classic TCM formulas, such as Liuwei Dihuang Pills, Qianjin Weijing Formula, Erxian Decoction, and Yishen Zhuangu Formula, and their key constituents, including puerarin and icariin, exhibit promising therapeutic potential for the prevention and treatment of osteoporosis. In addition, Glucosamine has been shown to significantly improve BMD and bone microarchitecture in osteoporotic mice, while also mitigating age-related changes and reducing apoptosis in bone tissue. By promoting osteoblast autophagy, glucosamine effectively delays the progression of osteoporosis in senile osteoporosis models.

Despite encouraging preclinical results, clinical evidence supporting the efficacy and safety of natural compounds for osteoporosis remains limited. Several factors contribute to this gap. First, ethical and regulatory constraints make it difficult to test these compounds in humans without extensive preclinical safety data. Second, limited funding, particularly for natural products that cannot be patented, reduces the feasibility of conducting large, randomized controlled trials. Third, osteoporosis trials typically require long-term follow-up and large sample sizes to adequately assess safety and efficacy. To address these challenges, future research should prioritize well-designed early-phase clinical trials to evaluate safety, optimal dosing, and pharmacokinetics of promising natural compounds.

From a pharmacological perspective, natural compounds such as flavonoids, terpenoids, saponins, alkaloids, and polysaccharides exhibit diverse and complementary effects on bone health. These bioactive compounds contribute to the prevention and treatment of osteoporosis through various mechanisms, such as regulating bone metabolism pathways, promoting osteogenesis, inhibiting bone resorption, and mitigating bone loss. To further highlight the novelty of this review, we compared our findings with those of reviews published over the past 5 years. While several reviews have summarized the antiosteoporotic potential of natural products, most either focus on a specific compound class or fail to integrate signaling mechanisms, clinical relevance, and compound sources. In contrast, our review provides a comprehensive overview of the mechanistic actions, pharmacological classifications, and research progress of representative natural compounds, effectively bridging the gap between basic research and clinical application and offering a more systematic, translational perspective.

Statement of ethics

None declared.

Conflict of interest statement

The authors declare that they have no conflicts of interest with regard to the content of this report.

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Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Author contribution

Writing—original draft: Ziyi Duan, Lan Jiang; Data curation: Wenhao Zhou, Yingjie Cai, Min Zhong, Jian Mao; Conceptualization: Lan Jiang; Writing—review and editing: Ziyi Duan, Lan Jiang.

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