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REVIEW

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Natural traditional Chinese medicine products: emerging therapeutic targets for the treatment of osteoporosis

Bo Liu[1†], Xue Mao[2†], Zhe-Jian-Yi Gao[2*] and Huan Wang[3*]

Abstract

Osteoporosis is a systemic metabolic degenerative bone disease characterised by decreased bone mass, impaired bone microstructure, weakened bone strength and susceptibility to fracture. In China, the prevention and treatment of osteoporosis is faced with a high disease prevalence rate but low awareness, diagnosis and treatment rates. Bone resorption inhibitors and bone formation promoters often dominate osteoporosis treatment. Although conventional drugs can alleviate symptoms and reduce fracture risk, they often come with musculoskeletal, allergic and digestive side effects. Natural traditional Chinese medicine (TCM) products, known for their multi-targeting, high safety, efficacy and low cost, have been widely used in the treatment and prevention of osteoporosis in recent years and have gradually been recognised by many experts locally and abroad. This paper summarises recent research progress on natural TCM products in preventing and treating osteoporosis and provides a theoretical and experimental basis for the development of new drugs and the improvement of osteoporosis management.

Keywords Osteoporosis, Osteoblast, Osteoclast, Natural products, Traditional Chinese medicine

Introduction

Osteoporosis is a chronic metabolic bone disease characterised by decreased bone mass, impaired bone tissue microarchitecture, diminished bone strength and increased fracture risk [1]. In traditional Chinese medicine (TCM), osteoporosis is categorised as 'bone impotence' or 'bone paralysis' [2], with the understanding that although the condition is primarily located in the bones, there is a close relationship with kidney, spleen and liver functions. According to TCM theory, kidney essence provides the foundation for bone health, the liver ensures smooth blood circulation to nourish bones and the spleen transforms nutrients for bone maintenance. Osteoporosis is characterised by bone withering and marrow reduction, with kidney essence deficiency as the root cause, and manifestations of blood stasis, paralysis and loss of bone vitality. Its onset is believed to relate to insufficient innate constitution and acquired injuries from external factors. At present, it is understood that the pathogenesis of osteoporosis involves various mechanisms, but the essential feature is the disruption of bone remodelling. Osteoblasts synthesise various bone matrix proteins and play a crucial role in bone formation, whereas osteoclasts participate in bone resorption by removing mineralised bone matrix [3–6].

[†]Bo Liu and Xue Mao contributed equally to this work.

*Correspondence:
Zhe-Jian-Yi Gao
gao_zhe_jian_yi@outlook.com
Huan Wang
wang6688happy@21cn.com
[1] Department of Orthopedics, The Fourth People's Hospital of Shenyang, 20 Huanghe Dajie, Huanggu District, Shenyang 110031, Liaoning, China
[2] Department of Orthopedics, Fushun Hospital of Chinese Medicine, No.9, East 6th Road, Zhanqian Street, Xinfu District, Fushun 113000, Liaoning, China
[3] Department of Orthopedics, Liaoning University of Traditional Chinese Medicine, 79 Chongshan Road, Huanggu District, Shenyang 110847, Liaoning, China

The balance between these two cellular activities maintains the continuous bone remodelling process [7]. A 2018 epidemiological survey in China revealed that the prevalence of osteoporosis among individuals over 50 years old was 19.2%, and among those over 65 years old, the prevalence was as high as 32.0%. With the aging of the population, the incidence of osteoporosis is gradually increasing. However, there is a lack of awareness regarding the importance of osteoporosis prevention and treatment among the general population, which often causes them to miss the optimal time for treatment [8, 9]. Therefore, China faces challenges in addressing the high prevalence rate of osteoporosis and its low knowledge, diagnosis and treatment rates. Recent evidence by Bao et al. has further demonstrated genetic factors in Chinese postmenopausal women that may impact osteoporosis susceptibility, highlighting the need for more comprehensive screening and personalized preventive strategies [10].

Western medications currently used clinically to treat osteoporosis include bone formation enhancers, bisphosphonates, denosumab, receptor activator inhibitors, selective oestrogen receptor modulators and hormone replacement therapies, as suggested by international guidelines – including the 2022 Hormone Therapy Position Statement of The North American Menopause Society for the primary prevention of bone loss – as well as the dual-action drug sclerostin monoclonal antibody [11, 12] Although these medications may increase bone density and reduce the risk of fractures in patients, they are still associated with common adverse effects [11, 12] including gastrointestinal symptoms, osteonecrosis of the jaw, atypical femoral fractures and increased cardiovascular risks with prolonged use. Migliorini et al. conducted a comprehensive Bayesian network meta-analysis of 76 RCTs involving 205,011 patients to assess the efficacy and safety of commonly used drugs for postmenopausal osteoporosis, finding that denosumab reported the lowest rate of non-vertebral fractures, romosozumab the lowest rate of vertebral fractures, and ibandronate the lowest rate of hip fractures [13].

In recent years, TCM has achieved advances in medicine with its diverse efficacy, safety, effectiveness and cost-effectiveness, and has been widely used in the prevention and treatment of osteoporosis [14–16]. Traditional Chinese medicine approaches can complement modern management strategies by targeting multiple pathways simultaneously and potentially offering options for patients who cannot tolerate conventional therapies or experience limited efficacy. Therefore, this review explores the mechanisms and impacts of natural TCM products in preventing and treating osteoporosis to offer new insights for its management and drug development.

Materials and methods

A comprehensive literature search was conducted using PubMed, Web of Science, CNKI and Wanfang databases to identify relevant studies published between 2000 and 2023. The search terms included 'osteoporosis', 'traditional Chinese medicine', 'natural products', 'osteoblast', 'osteoclast' and 'bone metabolism', as well as specific names of TCM compounds. Studies were selected based on the following criteria: (1) original research or comprehensive reviews on natural TCM products for osteoporosis; (2) studies with clear experimental design and methodologies; (3) investigations that identified specific mechanisms of action; and (4) experimental models using cellular or animal models of osteoporosis. Studies with unclear methodologies, insufficient data or those not directly related to osteoporosis treatment mechanisms were excluded. The data extraction focused on the compound name, source, molecular characteristics, experimental models, mechanisms of action and therapeutic effects. For studies involving animal experiments, the inclusion of appropriate controls and the obtaining of ethical approvals were evaluated.

Osteoblasts and osteoporosis

Osteoblasts are derived from mesenchymal stem cells (MSCs). The inhibition of osteoblast differentiation and proliferation plays a crucial role in the development of osteoporosis. Under normal circumstances, osteoblast differentiation and proliferation maintain bone quantity and quality in the body. However, when these processes are hindered, it can result in bone loss and alterations in bone microstructure, ultimately leading to the progression of osteoporosis. In this section, the influence of natural TCM products on osteoblast function through various molecular mechanisms and signalling pathways is examined. The detailed effects and mechanisms of natural TCM products for the treatment of osteoblast-mediated osteoporosis are shown in Table 1.

Reduction of oxidative stress

Oxidative stress refers to the imbalance between the oxidation system and the antioxidant system in the body, which leads to the excessive production of oxides such as reactive oxygen species (ROS) and reactive nitrogen species, thus causing tissue cell damage [32]. When ROS is overproduced, the body activates defence mechanisms against oxidative stress, leading to the upregulation of antioxidant enzymes such as SOD and GSH within the cellular antioxidant defence system to eliminate ROS molecules [33].

Having antioxidant effects, GSH can prevent cell damage caused by ROS. Moreover, increased GSH levels can enhance the expression of collagen type I alpha 1 (COL1

Table 1 The effects and mechanisms of natural products of TCM for the treatment of osteoblast-mediated osteoporosis

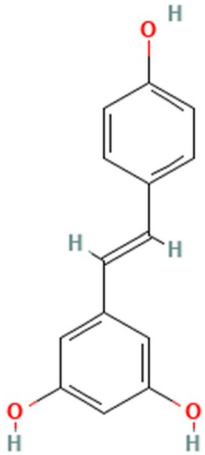
Natural Products/ Extracts	Natural Product/ Extract Source	Molecular Formula	Molecular Weight	Chemical Structure	CAS No.	Experimental Models	Mechanism of Action/ Effectiveness	References
Resveratrol	*Reynoutria japonica Houtt.*	$C_{14}H_{12}O_3$	228.243		501-36–0	Stimulation of MC3 T3-E1 cells with H2O2 induces a model of cellular senescence	Up-regulation of osteogenic gene expression such as ALP, COL-1, and Runx2 and reversal of H_2O_2-induced osteoblast damage	[17]
Total flavonoids of rhizoma drynariae	*Davallia mariesii Moore ex Bak.*	-	-	-	-	Constructing an osteoporosis rat model by ovariectomy	Up-regulation of Runx2 expression and amelioration of pathological bone trabecular injury through modulation of the signaling pathway Wnt/LRP5/β-catenin	[18]
Ginseng polysaccharides	*Panax ginseng C. A. Meyer*	-	-	-	-	Induction of osteoporosis rat model by bilateral ovariectomy	Maintains bone remodeling homeostasis by activating the Wnt3/β-catenin/Runx2 signaling pathway, decreasing TRAP-5b, and upregulating bone formation marker expression	[19]
Angelicin	*Psoralea corylifolia Linn.*	$C_{11}H_6O_3$	186.163		523-50–2	Osteocalcin overexpression in transgenic mice of the preosteoblastogenic cell line OCT1 cells; $BMP2^{loxp/loxp}$ mouse osteoblasts knocked down up to 80% of the osteoblast BMP2 gene by Ad-Cre lentivirus	Induces osteoblast proliferation and differentiation by activating the BMP2/Runx2/Osx signaling pathway and upregulating ALP expression levels	[20]

Table 1 (continued)

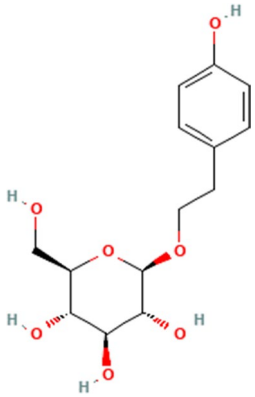
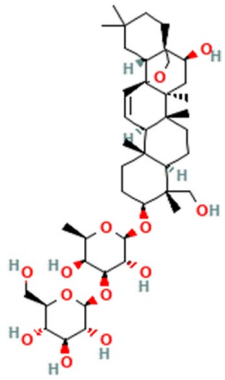
Natural Products/ Extracts	Natural Product/ Extract Source	Molecular Formula	Molecular Weight	Chemical Structure	CAS No.	Experimental Models	Mechanism of Action/ Effectiveness	References
Velvet antler polypeptides	*Cervi Cornu Pantotrichum*	-	-	-	-	Constructing an osteoporosis rat model by intramuscular injection of dexamethasone (2 mg-kg-1) into rats	Activation of SIRT1/FoxO1 signaling pathway attenuates oxidative damage and significantly elevates femoral BMD	[21]
Salidroside	*Rhodiola rosea Linn.*	$C_{14}H_{20}O_7$	300.304		10338-51–9	A type 2 diabetic osteoporotic rat model was constructed by intraperitoneal injection of STZ after 8 weeks of high-sugar and high-fat diet, followed by ovariectomy at 10 weeks.	Up-regulates serum SOD, GSH-Px levels and reduces ROS, MDA by activating FoxO1/β-catenin pathway	[22]
Saikosaponin A	*Bupleurum chinensis DC.*	$C_{42}H_{68}O_{13}$	780.982		20736-09–8	Construction of osteoporosis rat model by bilateral ovariectomy	Inhibition of oxidative damage through activation of the Keap1/Nrf2/ARE signaling pathway	[23]

Table 1 (continued)

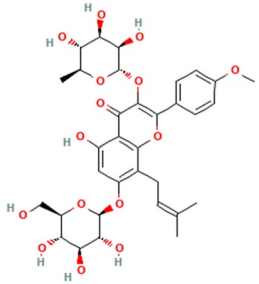
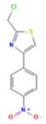
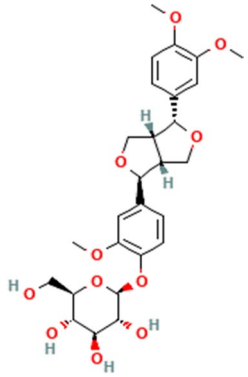
Natural Products/ Extracts	Natural Product/ Extract Source	Molecular Formula	Molecular Weight	Chemical Structure	CAS No.	Experimental Models	Mechanism of Action/ Effectiveness	References
Icariin	*Epimedium brevicornu Maxim.*	$C_{33}H_{40}O_{15}$	676.662		489-32–7	Bilateral ovariectomy constructed osteoporosis rat model	Up-regulation of serum OC and BALP expression and down-regulation of serum TRAP and NTX-I expression maintained bone remodeling homeostasis, and increased autophagy level and inhibited cell apoptosis	[24]
Astragalus polysaccharide	*Astragalus membranaceus (Fisch.) Bunge*	$C_{10}H_7ClN_2O_2S$	254.69		89250-26–0	Osteoblasts differentiated from bone marrow mesenchymal stem cells	Promoting osteoblast autophagy, proliferation, differentiation, and increased BMD through activation of the PI3 K/Akt/mTOR signaling pathway	[25]
Phillyrin	*Forsythia suspensa (Thunb.) Vahl*	$C_{27}H_{34}O_{11}$	534.552		487-41–2	Dexamethasone induced autophagy and apoptosis of osteoblasts in mouse MC-3 T3-E1 osteoblasts	Promotes autophagy and inhibits apoptosis through activation of the PI3 K/Akt/mTOR signaling pathway	[26]

Table 1 (continued)

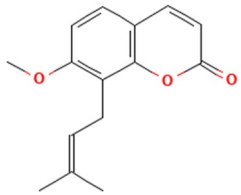
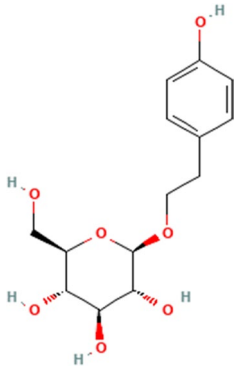
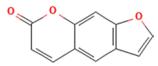
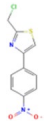
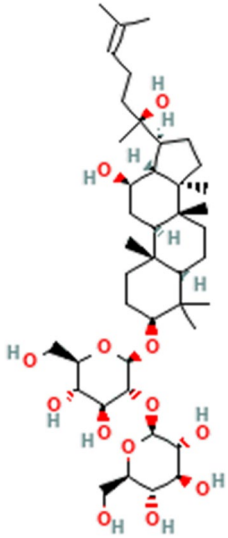
Natural Products/ Extracts	Natural Product/ Extract Source	Molecular Formula	Molecular Weight	Chemical Structure	CAS No.	Experimental Models	Mechanism of Action/ Effectiveness	References
Osthole	*Cnidium monnieri (Linn.) Cuss.*	$C_{15}H_{16}O_3$	244.286		484-12–8	Constructed osteoporosis rat model with bilateral ovarian removal	Down-regulates TRAP-5b levels and promotes blood calcium, blood phosphorus deposition and osteoblast proliferation through activation of the PI3 K/Akt signaling pathway	[27]
Salidroside	*Rhodiola rosea Linn.*	$C_{14}H_{20}O_7$	300.304		10338-51–9	mouse primary osteoblasts	Activates HIF-1α/VEGF, ANGPTL4, and IL-6 signaling pathways to promote osteoblast differentiation	[28]
Psoralen	*Psoralea corylifolia Linn.*	$C_{11}H_6O_3$	186.163		66–97–7	Establishment of postmenopausal osteoporosis model in SD rats by Spaying ovarieotom-y	Regulates PI3 K/Akt/mTOR signaling pathway and upregulates, OC, PINP, BMP2, and VEGF expression	[29]
Astragalus polysaccharide	*Astragalus membranaceus (Fisch.) Bunge*	$C_{10}H_7ClN_2O_2S$	254.69		89250-26–0	MC-3 T3-E1 osteoblasts	Inhibits osteoblast apoptosis and promotes differentiation by modulating the AMPK/eNOS signaling pathway	[30]

Table 1 (continued)

Natural Products/ Extracts	Natural Product/ Extract Source	Molecular Formula	Molecular Weight	Chemical Structure	CAS No.	Experimental Models	Mechanism of Action/ Effectiveness	References
Ginsenoside Rg3	*Panax ginseng C. A. Meyer*	$C_{42}H_{72}O_{13}$	785.013		14197-60–5	23-month-old female rats were selected to simulate the state of bone loss in the elderly as an osteoporosis model	Activates AMPK/mTOR signaling pathway, decreases PICP level, elevates OC, Beclin-1 and LC3-II expression, and promotes osteoblast autophagy	[31]

A1), OC and alkaline phosphatase (ALP) while inhibiting the ROS/nuclear factor kappa-B (NF-κB) signalling pathway. This leads to promoting osteoblast differentiation and inhibiting RANKL-mediated osteoclastogenesis [34, 35], thus maintaining bone remodelling homeostasis. Therefore, mitigating osteoblast damage and bone destruction resulting from oxidative stress injury can be achieved by enhancing the activity of antioxidant enzymes such as SOD and GSH (Fig. 1).

Alkaline phosphatase and bone ALP (BALP) are some of the most common indicators of bone formation and bone turnover. Bone ALP, a specific surface glycoprotein secreted by osteoblasts, reflects the formation and activity of osteocytes, making it a key marker for assessing bone formation and transformation. Tartrate-resistant acid phosphatase (TRAP), a glycoprotein produced by osteoblasts, macrophages and dendritic cells, indicates bone resorption and osteoblast activity, with TRAP-5b being particularly significant [36]. Serum osteocalcin (OC) is a non-specific collagen secreted by osteoblasts, and its content responds to osteoblast activity, making it a sensitive indicator of bone formation [37]. Osteopontin (OPN) and bone sialoprotein (BSP), members of the small integrin-binding ligand N-linked glycoprotein family in mineralised tissues, are the major phosphorylated proteins in bone and important markers of osteoblasts [38]. Osterix (Osx), also known as Sp7, is specifically expressed in osteoblasts and osteoclasts and is a downstream factor of Runt-related transcription factor 2 (Runx2), and it plays a role in the differentiation and maturation of osteoblasts [39].

It is important to note that bone turnover markers not only serve diagnostic purposes but are also valuable for identifying early responses to anti-resorption therapies, allowing more timely adjustments to treatment strategies. This application is particularly well-documented in studies by Migliorini et al., who conducted systematic reviews examining the role of biomarkers in monitoring therapy response in postmenopausal osteoporosis. [40, 41].

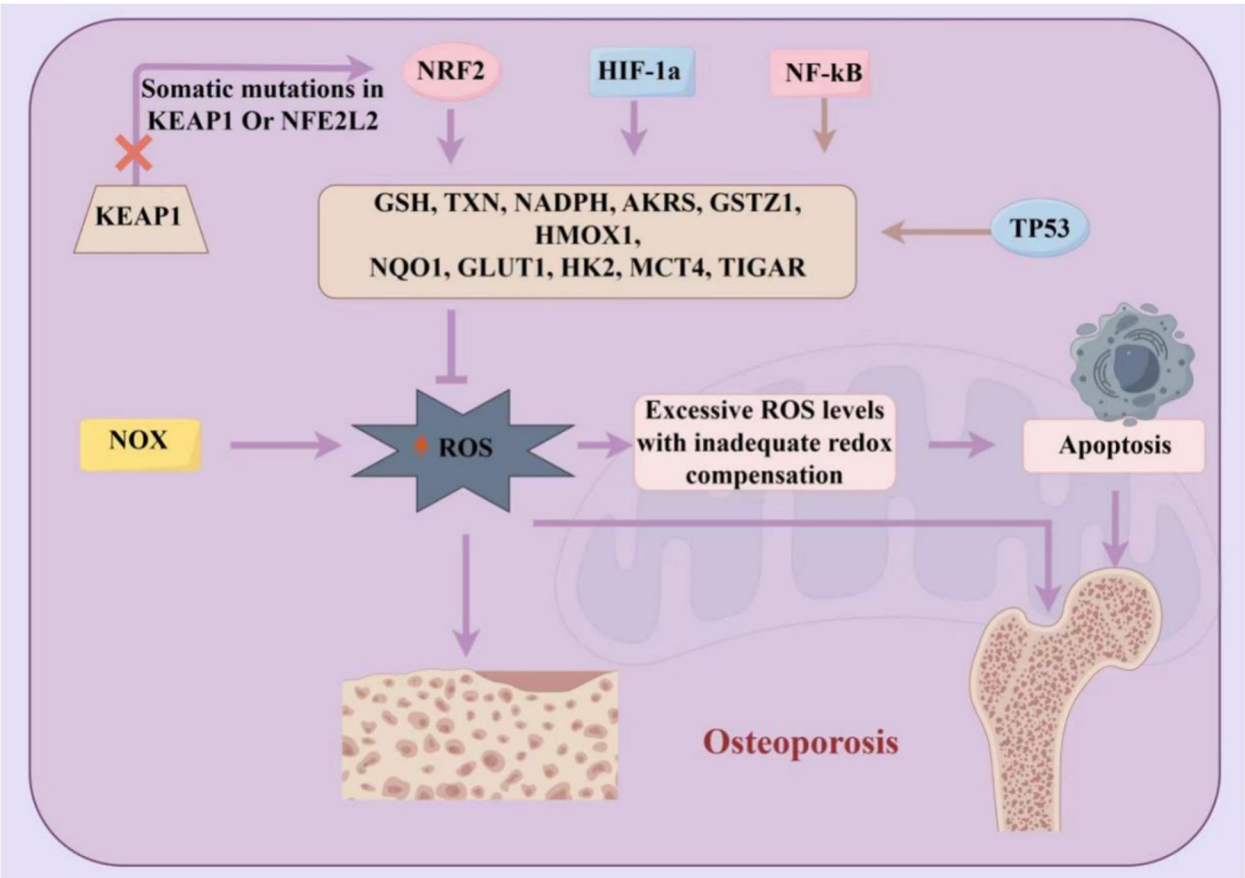


Fig. 1 The role of oxidative stress in osteoporosis. (TXN: thioredoxin; AKR: aldo-keto reductase; GSTZ1: Glutathione S-transferase zeta 1; HK2: hexokinase 2; MCT4: monocarboxylate transporter 4; TIGAR: P53-induced glycolysis and apoptosis regulator.)

Runt-related transcription factor 2

Runt-related transcription factor 2 has diverse functions and plays an important role in maintaining the balance of bone metabolism in osteoporosis by regulating the differentiation, development and growth factor expression of osteoblasts [42, 43]. It up-regulates osteoblast-related genes such as COL1 A1, ALP, BSP, BGLAP and OC [44]. Additionally, Runx2 induces the expression of Osx and Wnt signalling pathways, which affect osteoblast differentiation and chondrocyte maturation, ultimately promoting bone formation [45, 46]. Xue et al. [17] studied the stimulation of mouse embryonic osteoblast precursor (MC3 T3-E1) cells with H_2O_2, thus inducing a cellular senescence model. The results showed that 0.1 μmol/L resveratrol could reverse the inhibitory effect of H_2O_2 on ALP activity in osteoblasts and promote the expression of osteogenic genes collagen-I (COL-I), Runx2 and OC mRNA. At the same time, resveratrol could reduce the elevation of β-galactosidase activity induced by H_2O_2. The conclusions suggested that resveratrol promoted osteogenic differentiation and reversed H_2O_2-induced osteoblast damage through the upregulation of ALP and osteogenic genes such as COL-I and Runx2, exerting a protective effect against senescence.

Wnt-related signalling pathway The Wnt signalling pathway influences osteoporosis processes by affecting bone variables through multiple molecular pathways [47, 48]. The Wnt/LRP5/β-catenin pathway is a classical bone metabolism regulatory pathway. When the Wnt pathway is activated, it binds to LRP5/6 and Frizzled receptors to form a complex, which stimulates the cytoplasmic transcriptional regulator β-catenin to enter the nucleus and bind to members of the Lef1/Tcf family of nuclear proteins to activate the transcriptional expression of downstream target factors, such as Runx2, C-myc and other transcriptional expressions. This promotes the secretion of COL-I and OC from MSCs and chondrocytes, causing them to differentiate into osteoblasts and exerting anti-osteoporosis effects [49, 50]. The decline in ovarian function and oestrogen levels post-menopause can disrupt bone metabolism, resulting in damage to bone tissue microstructure, loss of bone mass and decreased bone density [51]. Zhang et al. [18] constructed an osteoporosis model by ovariectomy and administered total flavonoids of Rhizoma drynariae (TFRD) via gavage to upregulate the mRNA expression levels of Wnt3α, LRP-5, β-catenin and Runx2, as well as the protein expression of Wnt3α, LRP-5 and β-catenin in the tibia tissue of rats with osteoporosis, thereby attenuating the structural damage of bone tissue. Li et al. [19] resected the bilateral ovaries of rats to induce an osteoporosis model, and following gavage intervention with ginseng polysaccharides, compared with the model group, the levels of BMD, maximal stress and maximal load increased in rats with osteoporosis. Additionally, serum BALP, OC, osteoclastogenesis inhibitory factor (OPG), P3+, Ca^{2+} content and bone tissue Wnt3, β-catenin and Runx2 expression were significantly upregulated, whereas TRAP-5b content decreased. In conclusion, ginseng polysaccharides improved osteoporosis by activating the Wnt3/β-catenin/Runx2 signalling pathway and regulating the balance of bone formation and bone resorption.

Transforming growth factor beta-related signalling pathway

By regulating osteogenesis-related genes and recruiting osteoblasts to the bone surface, transforming growth factor beta (TGF-β) plays a crucial role in promoting osteoblast differentiation, bone formation and bone repair [52–54]. The Smad family of proteins are intracellular signalling proteins that are directly involved in TGF-β signalling, as well as members of several protein families such as BMP, which regulate osteoblast and osteoclast functions and play key regulatory roles in bone remodeling [55, 56]. A member of the TGF-β superfamily, BMP is essential for limb development and cartilage growth [50], and BMP2 is a potent growth factor with bone and cartilage formation-inducing effects [57]. Moreover, BMP/Smads is a classical pathway regulating bone metabolism, which is mainly regulated by BMP2 activation of Smad-1, 5, 8, inducing the expression of Runx-2 downstream gene osteoblast-specific transcription factor (Osx) to regulate osteoblast differentiation and maturation. Zhang et al. [20] used the osteocalcin-overexpressing transgenic mouse preosteoblast cell line, OCT1, as the research model and intervened by adding angelicin. The study showed that angelicin could promote osteoblast proliferation and upregulate the expression levels of osteoblast BMP2 mRNA, Runx2 and Osx proteins and mRNAs, with the effect observed at a low concentration of 10μg·mL^{-1}. In a further study, BMP2 gene knockout was achieved by 80% in osteoblasts of BMP2 loxp/loxp mice using Ad-Cre lentivirus. After administering 10μg·mL^{-1} angelicin, the expression of Runx2 and Osx genes in osteoblasts was promoted, and the expression level of ALP was upregulated. However, its effect was partially attenuated in BMP2-deficient osteoblasts. The results demonstrated that angelicin could induce osteoblast proliferation and differentiation through the activation of the BMP2/Runx2/Osx signalling pathway in a BMP2-dependent manner.

Silencing information regulator 1/Forkhead box O1-related signalling pathway Silencing information

regulator 1 (SIRT1) is a key factor in helping cells defend against oxidative stress, and it plays an important role in maintaining the balance between bone formation and bone resorption [21, 58]. Forkhead box O (FoxO) is a family of transcription factors containing four members: FoxO1, FoxO3, FoxO4 and FoxO6, with FoxO1 being widely expressed in bone and acting through deacetylation by SIRT1 [59]. Silencing information regulator 1 can promote osteoblast differentiation by stimulating the activity of β-catenin, FoxO1 and Runx2 proteins and inhibit osteoclasts by inhibiting the NF-κB signalling pathway and promoting the expression of FoxO proteins. Chi et al. [60] constructed an osteoporosis rat model by intramuscular injection of dexamethasone (2 $mg{\cdot}kg^{-1}$) and found that treatment with velvet antler polypeptides led to increased femur bone mineral density, improved bone pathology and higher levels of key proteins such as SIRT1 and FoxO1. It was concluded that velvet antler polypeptides inhibit oxidative stress by activating the SIRT1/FoxO1 signalling pathway and promote osteogenic differentiation to exert osteoprotective effects. Wang et al. [22] constructed a type 2 diabetic osteoporosis (DOP) rat model by intraperitoneal injection of STZ in combination with ovariectomy and administered salidroside by gavage for intervention. The study revealed that salidroside reduced serum ROS and MDA levels and increased serum SOD and GSH-Px levels, as well as the expression of FoxO1 and β-catenin proteins in femur tissues of rats. The study demonstrated that salidroside could improve oxidative stress injury in rats with DOP by activating the FoxO1/β-catenin pathway and exerting osteoprotective effects.

Keap1/Nrf2/ARE-related signalling pathway The Kelch-like ECH-associated protein 1 (Keap1)/nuclear factor erythroid-2-related factor 2 (Nrf2)/antioxidant response element (ARE) signalling pathway serves as a crucial defence mechanism against oxidative stress. In osteoblasts, Nrf2 activates osteoblast-specific genes such as Dmp1, Mep and Sost while suppressing osteoclast expression, which is crucial for maintaining endosteal homeostasis [61]. It has also been reported that the activation of the Keap1/Nrf2/ARE signalling pathway prevents bone loss in osteoporosis [62, 63]. Recent research by Huang et al. has demonstrated that asperuloside, a natural iridoid glycoside, exerts protective effects against osteoporosis by promoting autophagy and regulating Nrf2 activation, further supporting the role of this pathway as a therapeutic target [64]. Guo et al. [23] constructed an osteoporosis rat model through bilateral ovary removal and administered saikosaponin A (SA) gavage intervention. The results showed that SA downregulated the cytoplasmic Keap1 protein and mRNA levels and upregulated the nuclear Nrf2, HO-1 and NQO1 protein and mRNA expression levels in osteoporosis femur tissues. Saikosaponin A reduced serum MDA content and significantly elevated SOD and CAT activities in rats with osteoporosis. Scanning of the distal femur of rats with osteoporosis by a micro-CT imaging system revealed that BMD, bone volume fraction (BV/TV), trabecular number (Tb.N) and trabecular thickness (Tb.Th) of the femur were significantly elevated after SA intervention. The maximum load, maximum deflection and elastic modulus of the rat femur were also significantly elevated in the SA group, as measured using the three-point bending test, and SA attenuated the trabecular structure damage of the femur in rats with osteoporosis. Moreover, ML385 (a Keap1/Nrf2/ARE signalling pathway inhibitor) was found to impair the inhibitory effects of SA on bone loss and oxidative stress in rats with osteoporosis. It can be concluded that SA could inhibit oxidative stress by activating the Keap1/Nrf2/ARE signalling pathway, attenuate bone microstructure damage and improve bone biological performance in rats with osteoporosis (Fig. 2).

Oxidative stress can lead to a decrease in osteoblast activity, an increase in osteoblast and osteoclast apoptosis and a decrease in the expression of key osteoblast differentiation markers such as COL1 A1 and ALP, ultimately hindering bone formation [65]. However, antioxidants can enhance BMD and support bone formation and mineralisation by maintaining GSH levels [66]. Natural TCM products can reduce oxidative damage, stimulate osteoblast proliferation and differentiation, and enhance bone formation by regulating key signalling pathways such as Wnt/β-catenin, Keap1/Nrf2/ARE, SIRT1/FoxO1/β-catenin and BMP2/Runx2/Osx.

Inhibition of apoptosis

Apoptosis is an active and highly organised mode of cell death, primarily controlled by the Bcl-2 family and the caspase family [63]. Caspase family enzymes, particularly caspase-3, are key markers for the onset of apoptosis. Mitochondria, crucial regulators of apoptosis, release cytochrome c (Cytc), activating downstream factors such as caspase-9 and caspase-3 to trigger a series of cascade reactions that lead to apoptosis [67]. The members include Bax, Bak, Bcl-2, Bcl-xL and other apoptosis-related genes. Bax and Bak promote apoptosis by increasing mitochondrial permeability to release Cytc, acting as pro-apoptotic genes, whereas Bcl-2 counteracts Bax to inhibit membrane permeability, reducing Cytc release and apoptosis and functioning as an anti-apoptotic gene [68]. Osteoblast apoptosis is governed by the caspase cascade and is closely linked to the excessive

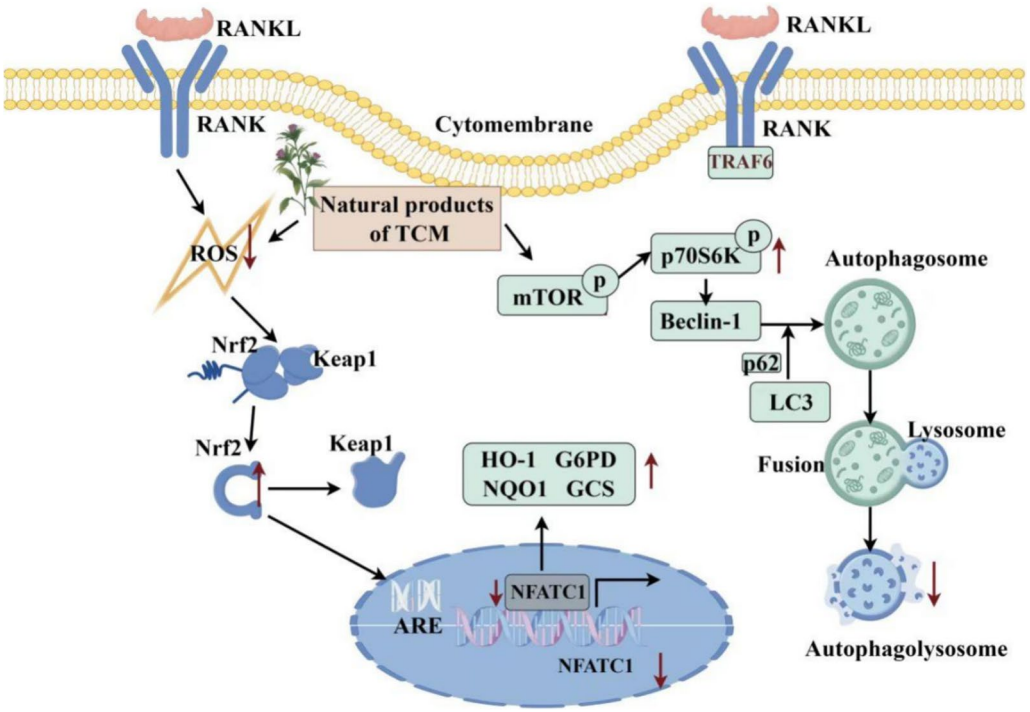


Fig. 2 Schematic illustration demonstrates the potential mechanism of action of Traditional Chinese Medicine (TCM) natural products in osteoporosis. (These natural products inhibit osteoclast generation by clearing ROS, leading to increased expression of antioxidant enzymes through activation of the Nrf2/Keap1 pathway. Additionally, they inhibit autophagy by activating the mTOR pathway. As a result, TCM natural products show promise as a potential treatment for bone diseases related to aging and oxidative stress, particularly osteoporosis.)

activation of the mitochondrial apoptotic pathway [69]. Autophagy, also known as type II programmed cell death, is a stress defence mechanism that maintains the stable state of the intracellular environment by removing abnormal and damaged proteins from the cell [70]. Autophagy and apoptosis are closely related and are regulated by upstream molecules Beclin 1 and Bcl-2-related proteins [71, 72]. The two main categories of LC3 are LC3-I and LC3-II; LC3-II can bind to autophagic vesicles to induce autophagic activation, making it a key biomarker of autophagy [73].

C-terminal telopeptide of type I collagen (CTX) and N-terminal telopeptide of type I collagen (NTX) are part of COL-I molecules, which are cleaved by osteoclasts during bone resorption. They are degradation products of mature collagen fibres in the extracellular matrix, proportional to the activity of osteoclasts, and are released into the bloodstream and excreted in the urine during bone resorption. They are often used as sensitive indicators of the rate of bone matrix degradation and bone resorption [74–76]. As reported by Garnero, monitoring changes in these markers can help predict long-term therapeutic outcomes and identify patients who may require alternative treatment approaches [77]. Among them, CTX, which is categorised into α-CTX and β-CTX, is negatively correlated with BMD and serves as a sensitive and specific marker of bone resorption [76–78]. He et al. [24] constructed an osteoporosis rat model through bilateral ovariectomy in female SD rats and, after treatment by intraperitoneal gavage with icariin, upregulated the protein expression levels of serum OC, BALP and bone tissues Beclin1, LC3-II and Bcl-2 while downregulating the protein expression levels of serum TRAP, NTX-I and bone tissues P62, caspase-3 and Bax. At the same time, icariin increased the femoral BMD and the biomechanical indexes of the femur (maximal load, maximal stress and stiffness) in rats with osteoporosis and improved the pathological changes of femoral trabecular bone. The experimental results showed that icariin increased the autophagy level to promote osteoblast differentiation and inhibited apoptosis, thus maintaining the metabolic balance between bone formation and bone resorption in de-ovulated rats.

While traditional Chinese medicine approaches offer promising alternatives, conventional interventions continue to evolve with important evidence emerging from clinical trials. Andersen et al. have recently proposed a protocol for a double-blind randomized sham-controlled clinical trial (VOPE2) to assess vertebroplasty's efficacy in patients with painful osteoporotic vertebral compression

fractures [79]. This rigorous methodological approach is essential for establishing evidence-based guidelines for fracture treatments in an aging population. Additionally, Shen et al. identified several risk factors for short-term residual low back pain following percutaneous kyphoplasty, including bone mineral density, preoperative injured vertebral kyphosis, preoperative thoracolumbar fascia injury, cement distribution type, and bone cement filling ratio. [80].

Phosphoinositide-3 kinase/protein kinase B-related signalling pathway Phosphoinositide-3 kinase/protein kinase B (PI3 K/Akt) is a classical and critical signalling pathway regulating cell proliferation, metabolism and apoptosis in vivo and often affects pro-apoptotic proteins such as Bad, mechanistic target of rapamycin (mTOR), NF-κB, caspase and GSK3β pathways involved in chondrocyte apoptosis, autophagy and inflammation [24, 71–81]. Protein kinase B is a downstream target of PI3 K that can affect osteoblast survival and differentiation by maintaining FoxOs in the cytoplasm or acting together with BMP2 [82]. The activation of the PI3 K/Akt/mTOR signalling pathway has been reported to play an active role in bone formation [83]. A member of the PI3 K family, mTOR induces autophagy and regulates osteoclast factors such as S6 K1 and Runx2 to promote bone formation [84]. Beclin-1 can be used as a marker for autophagy, and its deficiency is closely related to the occurrence of osteoporosis; P62 protein plays an important role in signalling pathways by interacting with different proteins, which can promote osteoclast autophagy and imbalance bone formation and resorption [85]. Sun et al. [25] used osteoblasts differentiated from bone marrow MSCs as culture study subjects and administered Astragalus polysaccharide for intervention. The results showed that, compared with the model group, the Astragalus polysaccharide treatment group exhibited enhanced cell proliferation and differentiation ability. The expression of p-AKT and p-mTOR was elevated in the osteoblasts, along with a certain reversal effect on inhibitors of the PI3 K/Akt/mTOR signalling pathway. Osteoblasts were increased, and the expression of Beclin-1, as well as the values of BMD, bone surface/bone volume, Tb.N and Tb.Th, were elevated. The expression of P62 and the value of trabecular separation (Tb.Sp) were also increased. The results showed that Astragalus polysaccharide promoted osteoblast autophagy, proliferation and differentiation, increased BMD and attenuated bone damage by activating the PI3 K/Akt/mTOR signalling pathway. Zhou et al. [26] used mouse MC-3 T3-E1 osteoblasts as the research model and first administered dexamethasone to induce autophagy and apoptosis of osteoblasts, followed by phillyrin treatment. The results showed that the OD570 value significantly increased, the intracellular Bcl-2 protein expression level was significantly elevated and the Bax, cleaved caspase-3 protein expression levels and apoptosis rate significantly decreased. Additionally, the expression levels of Beclin1, LC3-II/I, p-PI3 K/PI3 K, p-AKT/AKT and mTOR proteins, as well as the number of autophagic vesicles, were upregulated. The ALP activity was significantly elevated in the MC-3 T3-E1 cells. Therefore, phillyrin promotes osteoblast autophagy and proliferation and inhibits apoptosis by activating the PI3 K/Akt/mTOR signalling pathway to alleviate dexamethasone-induced cellular damage.

Bone tissue is rich in calcium and phosphorus. When bone resorption occurs rapidly, these minerals are released into the bloodstream and excreted in urine through the kidneys. In clinical settings, the 24-hour urinary calcium and urinary phosphorus excretion, as well as the urinary calcium/creatinine and urinary phosphorus/creatinine ratios, are commonly used to assess the levels of urinary excretion of these minerals [76]. Additionally, bone loss may be associated with low serum levels of P3+ and Ca2+, serving as an indirect indicator of osteoporosis severity [86]. The propeptide of type I procollagen (PINP), which is cleaved by protease during bone formation and excreted as a metabolite, reflects the rate of COL-I synthesis and osteogenic activity. Its serum level is a commonly used and sensitive indicator of the state of bone formation throughout the body [87, 88]. Pyridinoline and deoxypyridinoline (DPD) are stabilising collagen cross-linking molecules. When osteoclasts resorb the bone matrix, collagen fibres are hydrolysed and destroyed, resulting in free molecules that are released into the bloodstream and can be detected in urine, reflecting the level of bone resorption [76]. Li et al. [27] used bilateral ovariectomy to induce an osteoporosis rat model. Following gavage intervention with osthole, serum TRAP-5b was significantly reduced, and OC and ALP levels significantly increased in rats with osteoporosis. Urinary calcium/urinary creatinine, urinary phosphorus/urinary creatinine and DPD levels were significantly reduced. Additionally, p-AKT/AKT and p-PI3 K/PI3 K levels were significantly elevated in vertebral bone tissues. The whole-body BMD, isolated femur BMD and isolated vertebrae BMD were significantly elevated after 4 and 8 weeks of osthole treatment, and the elastic modulus and maximum load of femur and lumbar vertebrae were significantly raised in a dose-dependent manner in rats. Therefore, osthole exerts anti-osteoporosis effects by activating the PI3 K/Akt signalling pathway to promote calcium and phosphorus deposition in the blood and enhance osteoblast proliferation.

Vascular endothelial growth factor (VEGF) is both a major angiogenic factor and one of the osteogenic growth factors, significantly contributing to maintaining skeletal structure and promoting bone formation [9]. Hypoxia-inducible factor 1 alpha (HIF-1α) is a core transcription factor that regulates intracellular oxygen homeostasis and a key factor in activating VEGF transcription for angiogenesis and osteogenesis in osteoblasts. Its overexpression promotes bone vascularisation and osteogenesis [89]. Angiopoietin-like protein 4 (ANGPTL4) is the primary target gene downstream of HIF-1α, which enhances osteoblast proliferation and differentiation [90]. Interleukin (IL)−6, VEGF and ANGPTL4 are downstream target genes of HIF-1α, which can have beneficial effects on osteoporosis by enhancing bone angiogenesis and osteoblast proliferation [90–92]. However, IL-6 is now found to have regulatory effects on osteoblasts, osteoclasts, bone marrow adipocytes and osteocytes, and it only promotes the first stage of osteoblast differentiation while inhibiting the other stages [93–95]. Jin et al. [28] studied mouse primary osteoblasts (mOB) cultured with salidroside, which showed that salidroside had a promotional effect on mOB proliferation and upregulated osteoblast HIF-1α mRNA and VEGF, ANGPTL4 and IL-6 protein and mRNA expression. Further experiments gave the HIF-1α blocker YC-1 to mOB treatment for 1 hour, followed by the addition of salidroside intervention. The researchers found that the protein expression of HIF-1α, VEGF, ANGPTL4 and IL-6 was downregulated by the addition of YC-1 compared with the salidroside intervention group. The results indicated that salidroside promoted mOB proliferation by activating the HIF-1α/VEGF, ANGPTL4 and IL-6 signalling pathways. Moreover, existing studies have shown that VEGF expression is closely related to oestrogen levels in osteoblasts, and oestradiol (E2) can upregulate VEGF expression through the activation of the PI3 K/Akt signalling pathway to promote new bone formation and bone repair [96]. Chen et al. [29] established a postmenopausal osteoporosis model in SD rats through ovariectomy and administered psoralen via gavage. The results showed that femur and vertebrae bone mineral density, as well as serum levels of calcium ions, osteocalcin, PINP, BMP2 and VEGF, were significantly elevated, whereas the expression levels of PI3 K, Akt, mTOR proteins and mRNAs in femur tissues were reduced following psoralen intervention. Thus, psoralen promotes osteoblast differentiation and bone formation by modulating the PI3 K/Akt/mTOR signalling pathway.

AMPK-related signalling pathway Reports have confirmed that adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK) plays a crucial role in regulating cellular energy metabolism homeostasis. Moreover, AMPK is present in bone tissue and cells, with the AMPKα1 subunit being the primary catalytic isoform. Activation of AMPK promotes BMP2, endothelial nitric oxide synthase (eNOS) and OC expression and osteoblast differentiation while decreasing osteoblast RANKL expression and inhibiting osteoclastogenesis [97]. Wang et al. [30] used MC-3 T3-E1 osteoblasts as the research model and cultured them in DMEM medium containing Astragalus polysaccharide. The results showed that Astragalus polysaccharide enhanced cell proliferation viability, promoted the expression of osteogenic marker gene proteins ALP and OC, upregulated the expression of osteoblast Bcl-2 anti-apoptotic proteins and p-AMPK and eNOS proteins, and downregulated the expression of Bax and cleaved caspase-3 pro-apoptotic proteins in a dose-dependent manner. The results suggest that Astragalus polysaccharide may promote osteoblast proliferation and osteogenic marker protein expression by regulating the mitochondrial apoptotic pathway and AMPK/eNOS signalling pathway.

Adenosine 5'-monophosphate-activated protein kinase/mTOR is a classical autophagy signalling pathway, where AMPK negatively regulates mTOR to promote autophagy. This process involves increasing the expression of autophagy-related proteins LC3-II/I and Beclin1 while decreasing p62 levels, playing a crucial role in inducing osteoblast differentiation and mineralisation [98]. Procollagen type I carboxy-terminal peptide (PICP) is a key precursor for COL-I synthesis, constituting a significant portion of the bone's organic matrix and positively correlating with bone formation [99]. Ma et al. [31] selected 23-month-old female rats to simulate age-related bone loss as an osteoporosis model and administered ginsenoside Rg3 by gavage for treatment. This intervention elevated femoral BMD, BV/TV, Tb.N, Tb.Th and OC levels while reducing Tb.Sp and serum PICP levels in rats with osteoporotic. Additionally, ginsenoside Rg3 improved trabecular structure, upregulated AMPK mRNA and the p-AMPK/AMPK ratio and downregulated mTOR mRNA expression and the p-mTOR/mTOR ratio in the femoral bone marrow tissues of rats with osteoporotic rats, thereby increasing the expression of autophagy proteins Beclin-1 and LC3-II. These findings indicate that ginsenoside Rg3 enhances osteoblast autophagy, promotes osteoblast differentiation and stimulates bone formation by activating the AMPK/mTOR signalling pathway through AMPK phosphorylation.

In the context of aging, immune system disorders resulting from age-related oxidative stress and decreased oestrogen levels may accelerate osteoblast apoptosis and disrupt the balance of bone remodeling [100]. Natural

TCM products influence osteoblast apoptosis by regulating apoptosis-related signalling pathways such as PI3 K/Akt, AMPK/eNOS and AMPK/mTOR, as well as their interactions. Additionally, they modulate the mitochondrial pathway of caspases, Bcl-2 family proteins and other key targets.

Osteoclasts and osteoporosis

Although osteoblasts contribute to bone formation, as discussed in "Introduction" section, osteoclasts serve as the counterbalancing force in bone homeostasis, facilitating bone resorption and remodelling. These multinucleated cells, derived from the monocyte/macrophage lineage, play a critical role in maintaining skeletal integrity through coordinated bone turnover. Osteoclasts are multinucleated cells responsible for bone resorption in bone tissue. In normal conditions, the amount of bone resorbed by osteoclasts equals the amount of bone formed by osteoblasts. However, when people are experiencing menopause and aging, the degree of bone resorption is greater than bone formation [101], and the number of osteoclasts on the surface of the bone is abnormally increased, the activity is abnormally enhanced and excessive bone resorption occurs, leading to the occurrence of osteoporosis [102]. Most signals, hormones and transcription factors affecting osteoclast proliferation, differentiation and function are co-regulated by RANKL and its downstream receptors OPG and RANK [103]. An important signalling pathway, OPG/RANK/RANKL regulates the function of osteoclasts: RANKL is a key ligand for osteoclastogenesis, mainly expressed in osteoclast precursors; RANK is the receptor for RANKL; and OPG is the decoy receptor for RANKL, which inhibits osteoclastogenesis by blocking the binding of RANK and RANKL [101] and prevents the over-resorption of bone to maintain bone metabolic balance. Existing studies have identified tumour necrosis factor receptor-associated factor 6 (TRAF6) as a key factor in activating the RANKL/RANK signalling pathway [104]. When RANKL binds to the receptor RANK and recruits TRAF6, it promotes the activation of osteoclast key proteins and the expression of nuclear factor of activated T cells 1 gene (NFATc1) and c-Fos, which induces downstream activation of the NF-κB and PI3 K/AKT pathways, promoting osteoclast differentiation [105, 106]. The detailed effects and mechanisms of natural TCM products for the treatment of osteoclast-mediated osteoporosis are shown in Table 2.

Cheng et al. [107] used intraperitoneal injection of STZ to construct a DOP model and gave Polygonatum sibiricum polysaccharides via gavage intervention for 4–8 weeks. This upregulated the expression of OPG protein in femur tissues, downregulated the expression of RANKL and significantly ameliorated the pathological damage to the trabeculae of bone. It also significantly reduced the body mass of rats with DOP and dose-dependently increased the BMD value. From this experiment, it can be seen that P. sibiricum polysaccharides inhibited the proliferation and differentiation of osteoclasts and prevented excessive bone resorption by regulating the OPG/RANKL signalling pathway. Peng et al. [108] constructed an osteoporosis rat model through bilateral ovarian removal in SD rats and gave Danshensu via gavage. This upregulated the levels of serum OPG and bone tissue TGF-β1 protein, as well as p-Smad3/Smad3 in rats with osteoporosis, downregulated serum RANKL expression levels and elevated BMD, bone mineral salt content and femur biomechanical indices, including elasticity modulus, maximal load and yield load values in rats with osteoporosis. It is suggested that Danshensu regulates the OPG/RANKL signalling pathway by activating the TGF-β/Smad signalling, enhances bone mineralisation, promotes bone formation and mitigates bone loss and biomechanical damage caused by osteoporosis.

Nuclear factor kappa-B-related signalling pathway

A transcription factor in mammalian cells, NF-κB usually exists as homo-/heterodimers formed by p65 and p50. Under normal conditions, NF-κB p65 in the cytoplasm binds to the inhibitory protein IκBα to form a trimeric complex, keeping it in an inactive state. When stimulated by external pathological factors, IκB kinase is activated, dissociating the trimeric complex and thus activating NF-κB p65, which enhances bone resorption by up-regulating NOD-like receptor thermal protein domain-associated protein 3 (NLRP3) inflammatory vesicle responses [116]. It has been shown that ROS can activate NF-κB to participate in the body's oxidative stress response [117], whereas the activation of SIRT1 inhibits NF-κB signalling and attenuates oxidative damage and inflammatory responses [118]. Xu et al. [109] exposed mouse MC3 T3-E1 cells to a model of H_2O_2-induced cellular oxidative stress and found that intervention with 10 μmol·L^{-1} and a lower concentration of curcumin significantly inhibited H_2O_2-induced cytotoxicity and osteogenic dysfunction, enhanced the viability of the model cells and up-regulated the ALP activity and calcium levels; it also inhibited the expression levels of RANKL, IL-6, IκB-α and p-p65. Further experiments were conducted to construct an oxidative stress osteoporosis mouse model using the bilateral ovary removal method. Following intraperitoneal injection of curcumin, the test showed that the serum MDA content and NTX expression in the mice decreased, whereas GSH activity and PICP levels were up-regulated, which reduced oxidative damage, inhibited osteoclast function and promoted bone formation

Table 2 The effects and mechanisms of natural products of TCM for the treatment of osteoclast-mediated osteoporosis

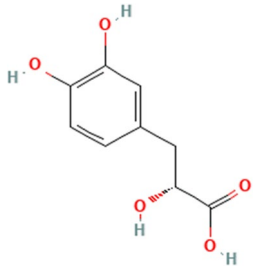
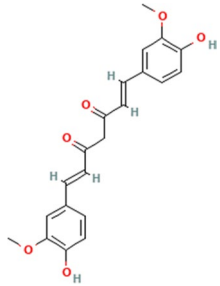
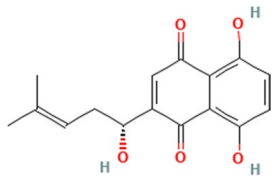
Natural Products/ Extracts	Natural Product/ Extract Source	Molecular Formula	Molecular Weight	Chemical Structure	CAS No.	Experimental Models	Mechanism of Action/ Effectiveness	References
Polygonatum sibiricum polysaccharides	*Polygonatum sibiricum Delar. ex Redoute*	-	-	-	-	Intraperitoneal injection of streptozotocin constructs diabetic osteoporotic rats	Regulates OPG/RANKL signaling pathway, reduces serum TRAP, decreases bone tissue calcium and phosphorus loss, and increases BMD	[107]
Danshensu	*Salvia miltiorrhiza Bunge*	$C_9H_{10}O_5$	198.17		76822-21–4	Construction of osteoporosis rat model by bilateral ovarian extraction	Regulation of the OPG/RANKL signaling pathway through activation of TGF-β/Smad signaling and elevation of BMD	[108]
Curcumin	*Curcuma longa Linn.*	$C_{21}H_{20}O_6$	368.380		458-37–7	Exposure of mouse MC3 T3-E1 cells to H_2O_2 induced cellular oxidative stress model; Bilateral ovary removal method for constructing an osteoporosis mouse model of oxidative stress	Inhibition of NF-κB signaling and down-regulation of RANKL, NTX expression and MDA content reverses oxidative damage	[109]
Shikonine	*Lithospermum erythrorhizon Sieb. et Zucc.*	$C_{16}H_{16}O_5$	288.295		517-89–5	The RAW264.7 cell line was used as a study subject, and the addition of dexamethasone induced the establishment of osteoporosis cell models; Injection of 2.5 $mg{\cdot}mL^{-1}$ dexamethasone into the legs of SD rats	Inhibition of RANKL/RANK/TRAF6 and its mediated NF-kB/MAPKs signaling pathway down-regulates serum CTX, Cathepsin K expression and osteoclast activity and increases BMD	[110]

Table 2 (continued)

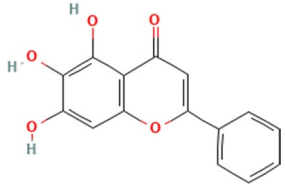
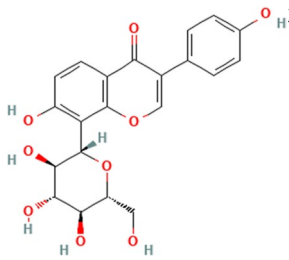
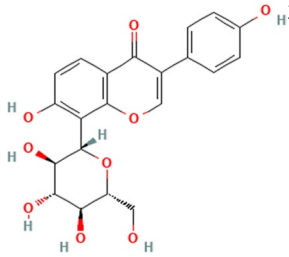
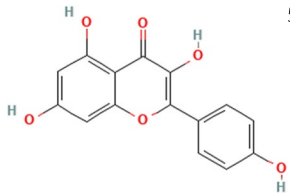
Natural Products/ Extracts	Natural Product/ Extract Source	Molecular Formula	Molecular Weight	Chemical Structure	CAS No.	Experimental Models	Mechanism of Action/ Effectiveness	References
Baicalein	*Scutellaria baicalensis Georgi*	$C_{15}H_{10}O_5$	270.237		491-67–8	Bilateral Oophorectomy Constructing osteoporosis Models	Inhibits the occurrence of Ferroptosis and maintains bone remodeling homeostasis by regulating the OPG/RANKL signaling pathway	[111]
Puerarin	*Puerariae Lobatae Radix*	$C_{21}H_{20}O_9$	416.38		3681-99–0	Ferroptosis was induced by culturing MC3 T3-E1 cells in high glucose medium, and an osteoporosis cell model was constructed by inducing with medium containing 10 mmol/L sodium β-glycerophosphate, 0. 1 μmol/L dexamethasone, and 50 mg/L VitC 4.	Activates SLC7 A11/GPX4 pathway, promotes GSH and SOD activities, inhibits MDA and ROS production, and attenuates Ferroptosis	[112]
Puerarin	*Puerariae Lobatae Radix*	$C_{21}H_{20}O_9$	416.38		3681-99–0	Bilateral ovarian removal constructed osteoporosis rat model	Regulation of PPARγ/Axin2/ Wnt signaling pathway down-regulates TRACP5b, PINP, IL-6, TGF-β, and TNF-α expression, inhibits adipocytogenesis, and regulates bone metabolism	[113]
Kaempferol	*Kaempferia galanga Linn.*	$C_{15}H_{10}O_6$	286.236		520-18–3	MC3 T3-E1 Subclone14 Cells	Activation of Wnt/β-catenin signaling pathway to maintain bone remodeling homeostasis	[114]

Table 2 (continued)

Natural Products/ Extracts	Natural Product/ Extract Source	Molecular Formula	Molecular Weight	Chemical Structure	CAS No.	Experimental Models	Mechanism of Action/ Effectiveness	References
Total flavonoids of rhizoma drynariae	*Davallia mariesii Moore ex Bak.*	-	-	-	-	Bilateral ovarian removal constructed osteoporosis rat model	Inhibits activation of Notch1/ Hes1/Prdx1 signaling pathway and attenuates oxidative stress injury; upregulates OPG and BMP-2 expression and inhibits osteoclastogen-esis	[115]

in rats with osteoporosis. The quantification from micro-CT scanning showed that curcumin treatment improved the structural damage of bone trabeculae and up-regulated BMD, Tb.N and Tb.Th values. Therefore, it can be concluded that curcumin can reverse bone damage and osteogenic dysfunction caused by oxidative stress by inhibiting NF-κB signalling.

MAPK-related signalling pathway

A member of the serine-threonine protein kinase family, MAPK comprises three subgroups: ERK, p38 and JNK. The MAPK cascade is activated through phosphorylation of p38, ERK1/2 and JNK, which regulate inflammatory and immune responses [119, 120] and promote osteoclastogenesis and activity [121]. Studies have shown that MAPK signalling is linked to NF-κB activation, controlling inflammatory responses and oxidative stress. The inhibition of ROS/MAPKs/NF-κB/NLRP3 activation has been observed to mitigate osteoclast proliferation and bone resorption capacity [116]. A lysosomal cysteine protease from the papain superfamily, Cat-K is a highly expressed and osteolytically active enzyme in osteoclasts, playing a crucial role in bone resorption by degrading OPN and osteonectin in the collagen and bone matrix [122]. Sang et al. [110] first used the RAW264.7 cell line as the study model and added dexamethasone to induce the establishment of an osteoporosis cell model. They then administered shikonin to reduce the number of TRAP-positive cells and the area of bone resorption. Further experiments on SD rats involved leg injection of 2.5 mg/mL dexamethasone to construct an osteoporosis rat model, with shikonin administered via leg injection for intervention. The results showed that, compared with the model group, shikonin inhibited serum CTX, Cat-K expression and osteoclast activity, increased BMD and reversed changes in bone tissue structure, such as trabecular thinning and empty bone fossa. Additionally, shikonin upregulated the expression levels of SOD and GSH and reduced the content of MDA, alleviating oxidative damage in rats with osteoporosis. It also inhibited the expression of RANK, RANKL, TRAF6, c-Fos and NFATc1 proteins, as well as the phosphorylation of IκB, p50, JNK, p65, ERK and p38. It was concluded that shikonin inhibited oxidative damage and osteoclast activity and ameliorated bone tissue damage caused by osteoporosis by inhibiting the RANKL/RANK/TRAF6 and its mediated NF-κB/MAPKs signalling pathway.

Ferroptosis

Ferroptosis is a form of iron-dependent non-apoptotic cell death characterised by the intracellular accumulation of iron ions, elevated levels of ROS and downregulation of GPX4 expression [123]. Oxidative stress and lipid peroxidation are key features of ferroptosis, with the system Xc^-/GSH/GPX4 axis playing a crucial role in eliminating lipid peroxidation. System Xc^- is a transporter protein composed of SLC3 A2 and SLC7 A11 that facilitates the synthesis of GSH [124]. Decreased expression of SLC7 A11 leads to reduced cellular GSH levels, increased ROS accumulation, decreased GPX activity (with GPX4 being a key mediator of ferroptosis) and ultimately the build-up of lipid peroxides that trigger ferroptosis [125]. Additionally, excessive iron and ROS levels can impair osteoblast function, weakening bone formation and promoting osteoclast differentiation. Therefore, targeting ferroptosis may offer a novel approach for the treatment of osteoporosis [125]. Li et al. [111] used bilateral ovariectomy to construct an osteoporosis model and then administered baicalein by gavage for treatment. They observed that baicalein positively influenced various markers associated with ferroptosis: it increased the expression of GSH and GPX4 while decreasing the levels of MDA and ROS. Additionally, baicalein upregulated the expression of OPG and Runx2 mRNA in femoral tissues while downregulating RANKL mRNA expression. This intervention led to an increase in femur and tibia BMD and BV/TV, as well as improvements in Tb.Th, Tb.N and connectivity density while reducing Tb.Sp and the structural model index in rats with osteoporosis. These findings suggest that baicalein modulated osteoblast and osteoclast proliferation and differentiation by affecting the OPG/RANKL signalling pathway and inhibiting ferroptosis, ultimately ameliorating bone pathological injuries in rats with osteoporosis. Chen et al. [112] induced ferroptosis by culturing MC3 T3-E1 cells with a high-glucose medium and constructed an osteoporosis cell model by exposing the cells to a medium containing sodium β-glycerophosphate, dexamethasone and VitC4. Subsequent puerarin intervention increased MC3 T3-E1 cell activity and the mRNA expression levels of ALP, Runx2, COL1 A1 and OPN. Puerarin improved the inhibitory effect on osteoblast proliferation and differentiation compared with the control group, leading to increased bone mineralisation. Additionally, it inhibited MDA and ROS production and attenuated the generation of high glucose-induced lipid peroxidation by promoting the activity of GSH and SOD and the expression of SLC7 A11 and GPX4 in osteoblasts. These findings suggest that puerarin inhibits high glucose-induced ferroptosis in osteoblasts by activating the SLC7 A11/GPX4 pathway (Fig. 3).

Wnt-related signalling pathway

Osteoblasts and adipocytes in the bone marrow cavity both originate from MSCs, with a negative correlation observed in their differentiation process. A decrease in the number and activity of osteoblasts often coincides

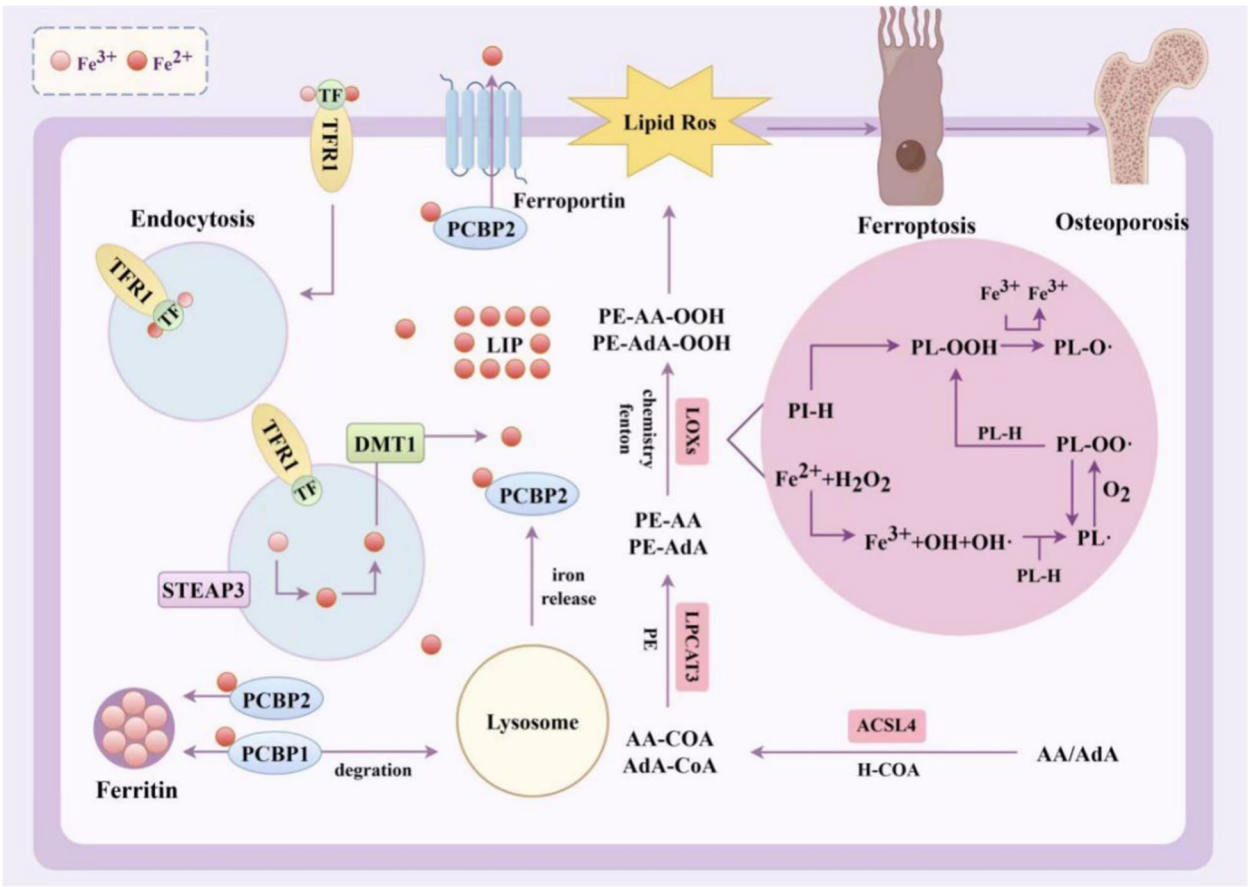


Fig. 3 Schematic diagram of mechanism of ferroptosis and osteoporosis

with an increase in adipocytes, known as the adipocyte excess hypothesis. This shift can lead to the apoptosis of osteoblasts, contributing to the development of osteoporosis [126]. Adipose tissue is now considered an immune organ, and adipogenesis is initiated by a cascade of key regulators, including peroxisome proliferator-activated receptor γ (PPARγ) and CCAAT/enhancer-binding protein (C/EBP) α, as well as mediated by various signalling pathways, such as Wnt, MAPK and insulin-like growth factor-1 [127]. The activation of the Wnt/β-catenin pathway can downregulate PPARγ and C/EBPs, inhibiting adipogenesis [128, 129]. An intracellular scaffolding protein, Axin2 inhibits Wnt/β-catenin signalling and negatively regulates β-catenin and BMP2/4, thereby inhibiting osteoblast proliferation and differentiation [130, 131]. Yang et al. [113] utilised an osteoporosis rat model induced by bilateral ovariectomy and treated with puerarin via intraperitoneal injections. The treatment significantly improved vertebral and femoral bone tissue damage, increased bone mineral density, reduced the levels of serum TRAP-5b, PINP, IL-6, TGF-β and TNF-α, attenuated inflammatory responses, upregulated β-catenin expression and downregulated PPARγ and Axin2 expression in bone tissues, which, in turn, facilitated the activation of the Wnt/β-catenin pathway. In this experiment, puerarin inhibited adipogenesis and regulated bone metabolism by modulating the PPARγ/Axin2/Wnt signalling pathway, improved the pathological damage of osteoporosis bone tissue and enhanced bone strength. Prostaglandin E2 (PGE2) is one of the main members of the prostaglandin family, and studies have shown that low concentrations of PGE2 promote osteoblast differentiation and proliferation, whereas high concentrations of PGE2 stimulate osteoclasts to promote bone resorption, which is involved in maintaining the dynamic balance of bone (Fig. 4) [132]. Dai et al. [114] intervened by giving kaempferol to MC3 T3-E1 subclone14 cells in culture. The results showed that cellular ALP content was increased, PGE2 and NO content was decreased and OPG, Wnt1 and p-β-catenin protein expression levels were upregulated, whereas RANKL protein expression levels were downregulated. The improvement in osteoclast inhibition and downregulation of Wnt1 and p-β-catenin protein expression were

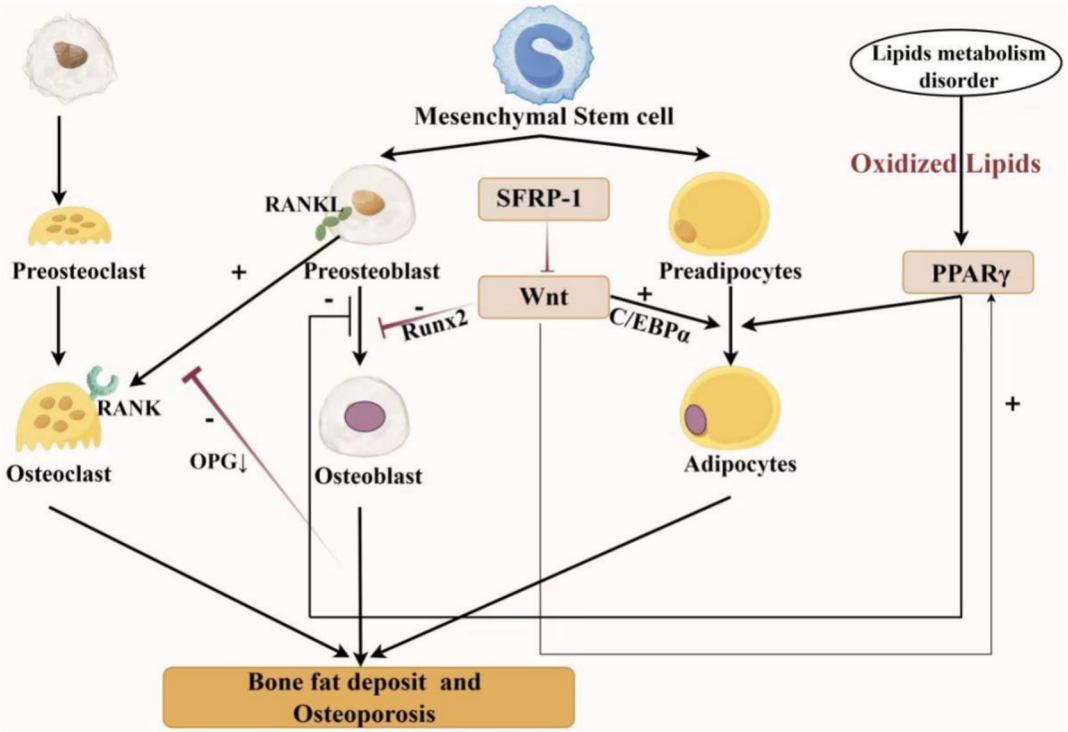


Fig. 4 Regulatory mechanism of the PPARγ/Wnt axis in osteoporosis. (Maintaining a delicate balance between adipocyte and osteoblast differentiation necessitates intricate communication among extracellular stimuli and a well-coordinated network of receptors and transcription factors within the nucleus. This network involves key pathways such as RANKL/RANK, Wnt/β-catenin, and PPARγ. Disruption in lipid metabolism can result in elevated levels of oxidized lipids, which, in turn, trigger adipocyte differentiation and hinder osteoblast differentiation through the activation of PPARγ.)

caused by the inhibition of the Wnt/β-catenin pathway. The results indicate that kaempferol regulates the balance between bone formation and bone resorption by activating the Wnt/β-catenin signalling pathway, promoting the proliferation and differentiation of osteoblasts and inhibiting osteoclast formation.

Notch1-related signalling pathway

The Notch signalling pathway is crucial in regulating various physiological and pathological processes, including cell differentiation, proliferation and apoptosis. Notch1 signalling typically hinders chondrocyte proliferation and differentiation, impacting bone formation and development [133]. Additionally, the Notch pathway influences bone remodelling by controlling osteoblast and osteoclast activities [134]. Part of the antioxidant enzyme system, PRDXs plays an antioxidant role in counteracting cytotoxicity due to ROS by scavenging H_2O_2 [135]. Lu et al. [115] induced an osteoporosis rat model with bilateral ovariectomy and then intervened with TFRD to attenuate the body weight loss of rats with osteoporosis and femoral morphostructural injuries such as bone trabecular breakage, loss and gap enlargement. This intervention also reduced their pathological scores, upregulated the expression of OPG and BMP2 in femoral tissues and increased serum SOD levels in rats. Additionally, TFRD reduced MDA and ROS levels in the serum and the expression of Notch1, Hes1 and PRDX1 proteins in femur tissues, suggesting that TFRD plays an anti-osteoporosis role by inhibiting the activation of the Notch1/Hes1/PRDX1 signalling pathway, alleviating oxidative stress injury, inhibiting osteoclastogenesis and bone resorption, promoting bone formation and regulating bone homeostasis.

Natural TCM products alleviate oxidative stress and inflammation by regulating signalling pathways such as OPG/RANK/RANKL, MAPKs/NF-κB/NLRP3 and Notch1/Hes1/PRDX1. They inhibit Ferroptosis by regulating the SLC7 A11/GPX4 pathway and reduce adipogenesis by regulating the PPARγ/Axin2/Wnt pathway, thus inhibiting osteoclast differentiation and bone resorption and improving osteoporosis symptoms.

Conclusion

Natural TCM products have been shown to mitigate oxidative damage, apoptosis and inflammatory responses; promote osteoblast proliferation, differentiation and mineralisation; and inhibit osteoclast differentiation, activity and bone resorption. This leads to improved bone metabolism through the modulation of relevant signalling pathways and inter-pathway interactions. Additionally, these products increase BMD, bone strength and biomechanical properties and help mitigate damage to bone microstructure. They play a role in anti-bone resorption, the promotion of bone formation and the alleviation of osteoporosis-induced bone injuries. Despite these promising findings, it is important to acknowledge the potential limitations of many of these natural compounds in current clinical practice. Most studies have been conducted in laboratory settings or on animal models, with limited large-scale clinical trials to validate their efficacy and safety in human populations. There is a clear need for larger, methodologically rigorous clinical studies to establish optimal dosing, long-term safety profiles and comparative effectiveness against standard osteoporosis treatments, as highlighted in recent evidence on modern management approaches [13].

Furthermore, it should be emphasized that the management of osteoporosis and related fractures, being the result of multifactorial processes, typically requires a personalized and multidisciplinary approach [136]. As demonstrated by Capozzi et al. and Al Taha et al., coordinated care involving multiple specialties can significantly improve outcomes for patients with osteoporotic fractures [137–139]. The complexity of bone metabolism and the variability in patient factors such as age, sex, comorbidities and genetic background necessitate individualized treatment strategies. Leeyaphan et al. recently proposed new cutoff values for simple clinical predictors to facilitate directive decision-making in osteoporosis screening for women. [139] Their cross-sectional study found that weight (cutoff value of 57.4 kg) was the most effective predictor of osteoporosis, followed by BMI (23.8 kg/m^2) and age (72 years). A comprehensive approach involving evidence-based pharmacological treatments to improve bone mineral density, along with multidisciplinary strategies for fragility fracture prevention and management, would likely yield the most beneficial outcomes for elderly patients with osteoporosis [140, 141].

In conclusion, although natural TCM products offer promising alternatives or complements to conventional osteoporosis treatments, their integration into mainstream clinical practice will depend on further validation through rigorous research and careful consideration of individual patient factors within a multidisciplinary treatment framework. Future studies should focus on identifying the most effective compounds, optimizing their formulations and determining their role within comprehensive osteoporosis management strategies.

Abbreviations

TCM	Traditional Chinese medicine
RANKL	Receptor activator of nuclear factor-κB ligand
TRAP	Tartrate resistant acid phosphatase
BMD	Bone mineral density
Cat-K	Cathepsin K
MSCs	Mesenchymal stem cells
ROS	Reactive oxygen species
H_2O_2	Hydrogen peroxide
SOD	Superoxide dismutase
GSH	Glutathione reductase
CAT	Catalase
MDA	Malondialdehyde
Prdxs	Peroxiredoxins
GPX	Glutathione peroxidase
NQO1	NADPH ubiquinone oxidoreductase
Runx2	Runt-related transcription factor 2
COL1 A1	Collagen type I alpha 1
ALP	Alkalinephosphatase
BALP	Bonealkalinephosphatase
OC	Osteocalcin
OPN	Osteopontin
BSP	Bone Sialoprotein
Osx	Osterix
TGF-β	Transforming growth factor β
BMP	Bone morphogenetic protein
COL-I	Collagen-I
TFRD	Total flavonoids of rhizoma drynariae
PGE2	Prostaglandin E2
Keap1	Kelch-like ECH-associated protein 1
Nrf2	Nuclear factor erythroid-2-related factor 2
ARE	Antioxidant response element
HO-1	Heme oxygenase-1
SA	Saikosaponin A
BV/TV	Bone volume fraction
Tb.N	Trabecular number
Tb.Th	Trabecular thickness
Cytc	Cytochrome c
AMPK	Adenosine 5′-monophosphate (AMP)-activated protein kinase
eNOS	Endothelial nitric oxide synthase
PI3 K	Phosphoinositide-3 kinase
Akt	Protein kinase B
mTOR	Mechanistic target of rapamycin
Tb.Sp	Trabecular separation/spacing
PINP	Propeptide of type I procollagen
DPD	Deoxypyridinoline
VEGF	Vascular endothelial growth factor
HIF-1α	Hypoxia-inducible factor 1 alpha
ANGPTL4	Angiopoietin-like protein 4
IL	Interleukin
MOB	Mouse primary osteoblast
PICP	Procollagen type I carboxy-terminal peptide
CTX	C-terminal telopeptide of type I collagen
NTX	N-terminal telopeptide of type I collagen
SIRT1	Silent information regulator 1
FoxOs	Forkhead Box O
NF-KB	Nuclear factor kappa-B
DOP	Diabetic osteoporosis
TNF-α	Tumor necrosis factor-α
NLRP3	NOD-like receptor thermal protein domain associated protein 3
TRAF6	Tumor necrosis factor receptor-associated factor 6
NFATc1	Nuclear factor of activated T cells 1 Gene
PPARγ	Peroxisome proliferator-activated receptor γ
C/EBP	CCAAT/enhancer-binding protein

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