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Exploring the potential role of genus *Sophora* in the management of osteoporosis: a phytochemical and biological review

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Bone metabolism is characterized by an interplay between the deposition of bone matrix and mineralization and the resorption process. Osteoporosis is a form of systemic metabolic bone condition that causes bone density to decline and its microarchitecture to deteriorate, increasing the risk of fracture owing to fragility. The underlying cause of this clinical disease lies in the imbalance in bone remodeling, in which bone resorption by osteoclasts predominates over bone creation by osteoblasts. Natural remedies have long been used to cure and prevent osteoporosis. Genus *Sophora* of the Fabaceae family comprises about 69 species that showed many pharmacological effects, including bone health preservation. The activity of *Sophora* sp. in maintaining bone health was attributed to its antioxidant, regenerative, and anti-inflammatory qualities. In this review, we focused on the therapeutic properties of the extracts and isolated compounds from the genus *Sophora* in maintaining bone health, with special emphasis on the management of osteoporosis.

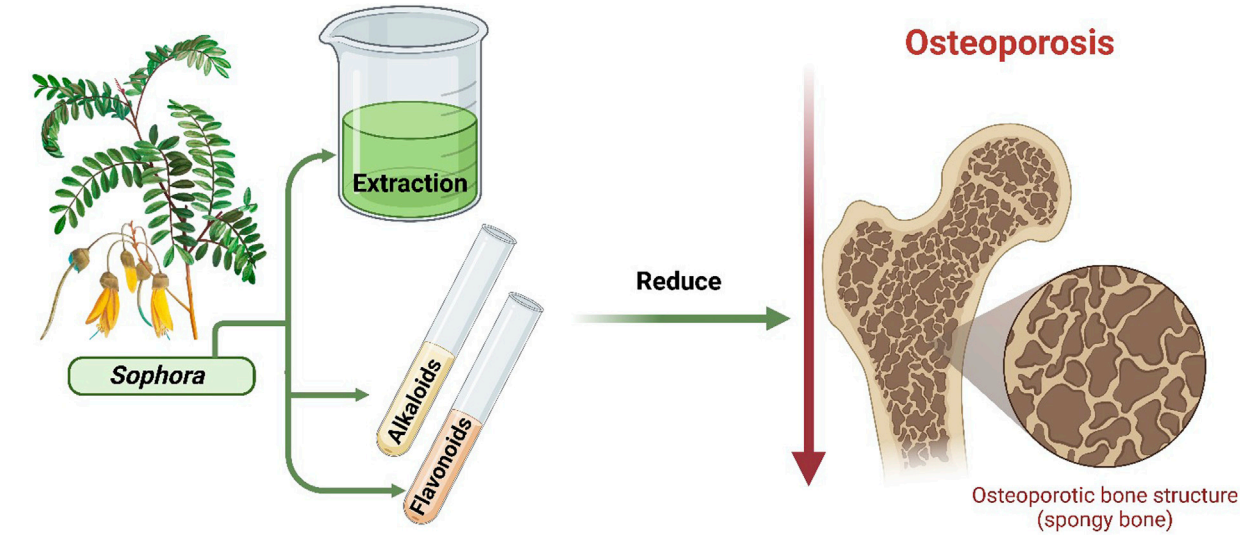
KEYWORDS

alkaloids, bone health, flavonoids, osteoporosis, *Sophora*

1 Introduction

The genus *Sophora*, subfamily Faboideae, family Fabaceae, contains around 69 species according to World Flora Online Data 2022 (https://powo.science.kew.org/) accessed in November 2023. These plants of this genus are distributed in tropical and temperate regions (Aly et al., 2019a). The abundant chemical constituents and potent pharmacological properties of *Sophora* sp. contribute to its diverse medicinal properties (Abd-Alla et al., 2014; Aly et al., 2019b; Boozari et al., 2019). *Sophora* sp. exhibited many biological activities, including anti-osteoporosis activity (Aly et al., 2020a; 2020b; 2021a; Chen Y. et al., 2023b).

The most common type of bone metabolism disorder is osteoporosis, characterized by chronic loss of trabecular bone and heightened vulnerability to fractures (Föger-Samwald et al., 2020). Osteoporosis is classified into two main categories, namely, primary and



GRAPHICAL ABSTRACT

secondary osteoporosis, based on its underlying causes. Primary osteoporosis primarily results from age-related factors and is commonly observed in individuals aged 50 and above. The most prevalent form of primary osteoporosis is postmenopausal osteoporosis (PMOP). Postmenopausal osteoporosis arises due to decreased estrogen production following menopause, leading to reduced bone mineral density (BMD). On the other hand, secondary osteoporosis is triggered by specific medications and medical conditions that result in a decline in BMD (Compston et al., 2019; Song et al., 2022).

The equilibrium between bone resorption, carried out by osteoclasts, and the formation of bone matrix, facilitated by osteoblasts, is meticulously regulated through a series of intricate and tightly controlled processes. These processes are crucial in maintaining mineral homeostasis and preserving bone mass (Kim et al., 2020). The imbalance between the formation and resorption of bones causes osteoporosis (Lei et al., 2023). Multiple transcription factors, including runt-related transcription factor 2 (Runx2) and osterix (Osx), along with essential developmental signals such as the Wingless-INT (WNT) signals, are recognized for their role in regulating osteoblast differentiation and function (Long, 2011). The differentiation and activity of osteoclasts are regulated by many factors, including cytokines, αVβ3 integrins, macrophage colony-stimulating factor (M-CSF), receptor activator of nuclear factor-κB ligand (RANKL), and its receptor RANK (Matsumoto and Endo, 2021; Song et al., 2022). A schema summarizing the cellular biology of osteoporosis is illustrated in Figure 1.

Natural alkaloids are currently used as anti-osteoporosis medications due to their high efficacy and low toxicity (Lin et al., 2022). *Sophora* alkaloids, including oxymatrine, matrine, sophocarpine, sophoridine, and aloperine, exhibited anti-osteoporosis effects through various pathways, particularly on the RANKL pathway. On the other hand, plant-derived flavonoids demonstrated protective effects against osteoporosis by promoting the survival, proliferation, and differentiation of cells involved in maintaining bone homeostasis (Bellavia et al., 2021). *Sophora* flavonoids and isoflavonoids, especially genistein, sophoricoside, sophorabioside, (2s)-2′-methoxykurarinone, 8-prenyl kaempferol, formononetin, maackiain, sophoraflavonoloside, nicotiflorin, and rutin showed anti-osteoporosis effects through several pathways. This review summarized *Sophora*'s isolated compound and prepared extracts from several species, which showed potential anti-osteoporosis efficacy. The discussed species of the genus *Sophora* include *S. japonica* L. (syn. *Styphnolobium japonicum)*, S. *flavescens* var. *flavescens*, *S. alopecuroides* L., *S. davidi* var. *davidi (Franch.) Skeels*, *S. secundiflora* (Ortega) Lag. ex DC. (syn. *Dermatophyllum secundiflorum*) and *S. tonkinensis* var. *tonkinensis* Gagnep.

The literature covered in this review spanned over the time range of 2010–2023. Several sources such as PubMed (http://www.ncbi.nlm.nih.gov/pubmed/), SciFinder (), Google Scholar (http://scholar.google.com/), and Science Direct (http://www.sciencedirect.com/) were consulted to retrieve relevant information. Keywords in this study are *Sophora* extract, *Sophora* compounds, Osteoporosis, Bone, and treatment.

2 Reported isolated compounds from *Sophora* sp. with potential effect on bone health

2.1 Flavonoids and isoflavonoids

Flavonoids and isoflavonoids are naturally occurring polyphenolic compounds extracted from higher plants. They are essential to the human diet (El-Nashar et al., 2022). They provide a wide range of physiological and ecological activities (Wang et al., 2020). They are usually present as glycosides, which accumulate in plant cell vacuoles. Flavonoids are produced via the phenylpropanoid metabolic pathway and consist of three rings (C6–C3–C6) identified as A, B, and C, with a total of 15 carbon atoms (Santos et al., 2022). They are divided into seven subclasses

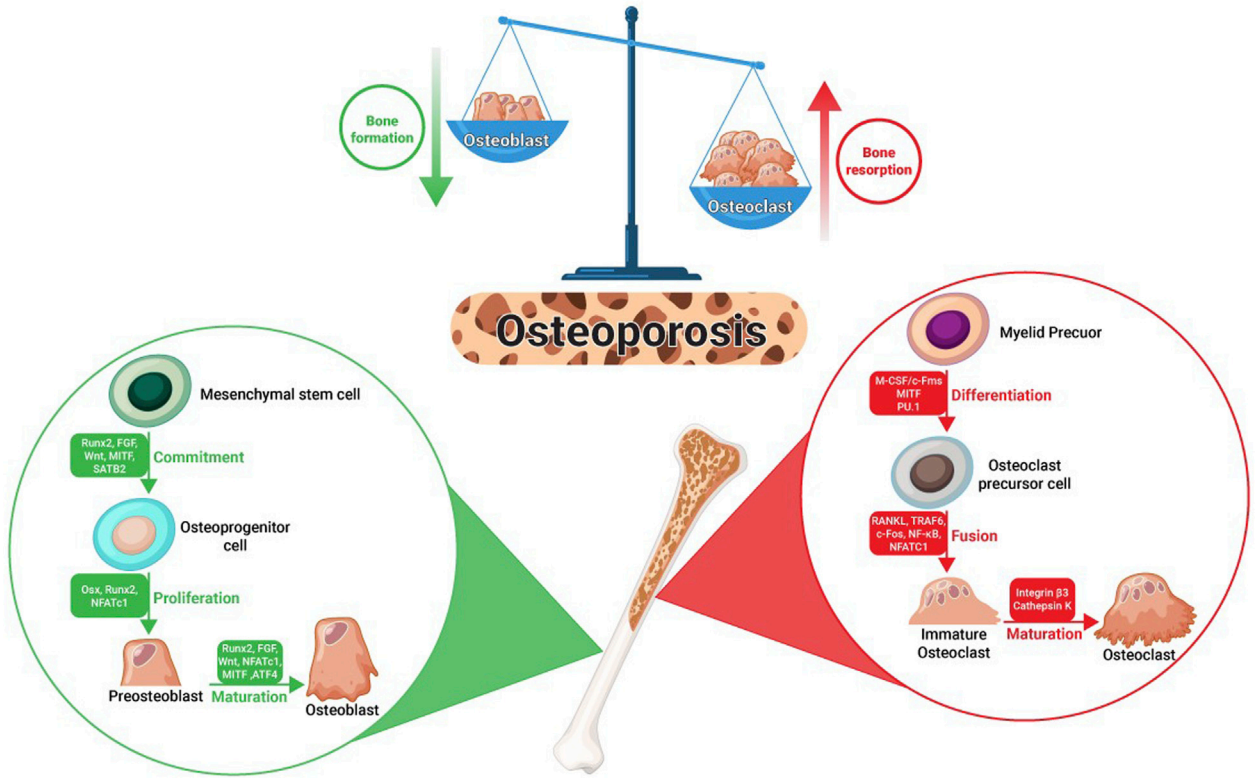


FIGURE 1
A schema summarizing the cellular biology of osteoporosis.

based on their structural differences, including anthocyanidins, flavanones, flavones, isoflavones, flavonols, flavones, and chalcones (Manzoor et al., 2020). This classification is based on the degree of oxidation in the central heterocycle (Shen et al., 2022; Chen S. et al., 2023). Flavonoid glycosides can undergo various modifications, including glycosylation and acylation, at the sites where methyl and hydroxy groups link to the other two rings (Shen et al., 2022). The biosynthetic pathway of flavonoids occurs at the point of convergence of the shikimate pathway and the acetate pathway. The first can produce *p*-coumaroyl-CoA, whereas the second pathway is responsible for regulating the elongation of C_2-chains (Li M. et al., 2022). They exhibit a wide range of pharmacological activities due to their anti-inflammatory, antioxidant, and anti-cancer effects, as well as their ability to stimulate the production of bones (Ramesh et al., 2021).

Genistein is a phytoestrogen that belongs to isoflavones. It possesses various pharmacological properties, including anti-inflammatory, anti-apoptotic, and anti-angiogenic effects (Nazari-Khanamiri and Ghasemnejad-Berenji, 2021). It is a tyrosine kinase inhibitor, which was reported to be dysregulated in the pathological development of certain pathways in osteoporosis, osteoarthritis, and intervertebral disc degeneration (IDD). Numerous signaling pathways, including MAPK, NF-κB, and NRF2/HO-1, contribute to genistein's regulatory role in preventing bone and cartilage disorders (Wu and Liu, 2022). Genistein isolated from *S. japonica* exhibited an anti-osteoporosis effect similar to soybean genistein. The study showed that the administration of a large amount of genistein from *S. japonica* to OVX rats at a dose of 4.5 or 9 mg/kg could prevent osteoporosis through many aspects, including improving bone density, bone mineral components like calcium, phosphorus, and magnesium, trabecular thickness, trabecular area percentage, and trabecular number (Wang et al., 2006).

An isoflavone called sophoricoside (genistein-4′-*β*-D-glucoside) was extracted from *S. japonica* (Kim and Lee, 2021a; 2021b). It exhibited many pharmacological properties, including estrogenic activity, anti-inflammatory, antioxidant, anti-diabetic, and immunomodulatory effects (Patel et al., 2020). A study was conducted to evaluate the estrogenic proliferative activities of seven isolated compounds including genistin, sophoricoside, sophorabioside, sophoraflavonoloside, genistein 7,4′-di-O-*β*-D-glucopyransoide, kaempferol 3-O-α–L-rhamnopyranosyl(1→6)*β*-D-glucopyranosyl(1→2)*β*-D-glucopyranoside, and rutin in the estrogen-dependent MCF-7 cell line. The findings of this study according to the profile of cytotoxicity, impact on membrane integrity, and estrogenic proliferative activity revealed that the most potent estrogenic compound was sophoricoside. Consequently, sophoricoside was chosen for additional *in vivo* study to investigate its anti-osteoporosis effect in comparison with estradiol as a positive control in ovariectomized rats *in vivo* at doses of 15 mg/kg and 30 mg/kg for 45 days. The results showed that sophoricoside increased the mechanical strength of bones. Additionally, it increased osteogenic biochemical markers such as serum alkaline phosphatase (ALP) and osteocalcin (OCN) levels and decreased acid phosphatase levels (Abdallah et al., 2014).

TABLE 1 ***Sophora*** **flavonoids and isoflavonoids with potential effects on bone health.**

Compound name	*Sophora* species	Mechanism of action and efficiency	Study type	Model	Refs
Sophoricoside	*S. japonica*	• Increased the mechanical strength of bones • Increased osteogenic biochemical markers such as serum ALP and OCN levels • Decreased acid phosphatase levels	*In vivo*	Ovariectomized (OVX) rat model	Abdallah et al. (2014)
Maackiain	*S. flavescens*	• Disrupted the F-actin belt structures in mature osteoclasts • Inhibited RANKL-stimulated protein levels and NFATc1 transcriptional activity • Inhibited Ca^{2+} oscillation levels, further suppressing gene expression associated with osteoclasts	*In vitro*	Bone marrow macrophage (BMM) cells	Liu et al. (2020)
(2S)-2′-Methoxykurarinone	*S. flavescens*	• Prevented mature osteoclastic bone resorption • Prevented RANKL-induced osteoclastogenesis of BMMs by downregulating Akt, p38, JNK, c-Fos, and NFATc1, leading to decreased TRAP and OSCAR expression	*In vitro*	Bone marrow cells (BMCs)	Kim et al. (2014)
8-Prenylkaempferol (8-PK)	*S. flavescens*	• Promoted osteoblast development and maturation by increasing BMP-2 expression, phosphorylating Smad1/5/8 and p38, and increased Runx2 nuclear translocation and transcription • Increased ALP activity, bone nodule formation, and upregulated OCN, OPN, and Coll 1 mRNA expressions	*In vitro*	MC3T3-E1 cells	Chiou et al. (2011a)
Genistein	*S. japonica*	• Increased bone density, bone mineral components like calcium, phosphorus, and magnesium, and trabecular thickness, area percentage, and volume	*In vivo*	OVX rat model	Wang et al. (2006)
Formononetin	*S. secundiflora and S. flavescens*	• Enhanced TBAs by increasing the activity of ALP.	*In vivo*	OVX rat model	Ha et al. (2010)
Genistein Sophoricoside Sophorabioside Sophoraflavonoloside Nicotiflorin Rutin	*S. japonica*	• Enhanced ALP activity in MC3T3-E1 cell groups	*In vitro*	MC3T3-E1 cells	Yang et al. (2020)

Kurarinone is a natural flavanone found in various plants. It exhibited several pharmacological properties, including chemoprevention, anticancer, antifungal, antibacterial, anti-corona virus, neuroprotective, antioxidant, and anti-inflammatory properties (Kumar et al., 2021). It is an active component of *S. flavescens* (Li Z. et al., 2022). Kim et al. isolated (2S)-2′-methoxykurarinone (MK) from *S. flavescens* roots, at a concentration of 20 μM. MK prevented mature osteoclastic bone resorption and RANKL-induced osteoclastogenesis of bone marrow macrophages (BMMs) in an *in vitro* study. The therapeutic effect was linked to the downregulation of Akt, p38, and JNK, as well as c-Fos and NFATc1, which decreased TRAP and OSCAR expression (Kim et al., 2014).

8-Prenylkaempferol (8-PK), a prenylated flavonoid extracted from *S. flavescens*, a Chinese herb with anti-inflammatory and antiviral effects (Chiou et al., 2011a). In MC3T3-E1 cells, 8-PK at different concentrations ranging from 1 to 20 μM promoted osteoblast development and maturation. The impact of 8-PK on cell maturation was mediated by boosting bone morphogenetic protein (BMP)-2 expression, phosphorylating Smad1/5/8 and p38, and promoting Runx2 nuclear translocation and transcription. 8-PK also increased ALP activity and bone nodule formation and upregulated the mRNA expressions of OCN, osteopontin (OPN), and type 1 collagen (Coll 1). As a result, 8-PK may be beneficial in boosting osteogenic activity, which is necessary for bone formation, however further *in vivo* and

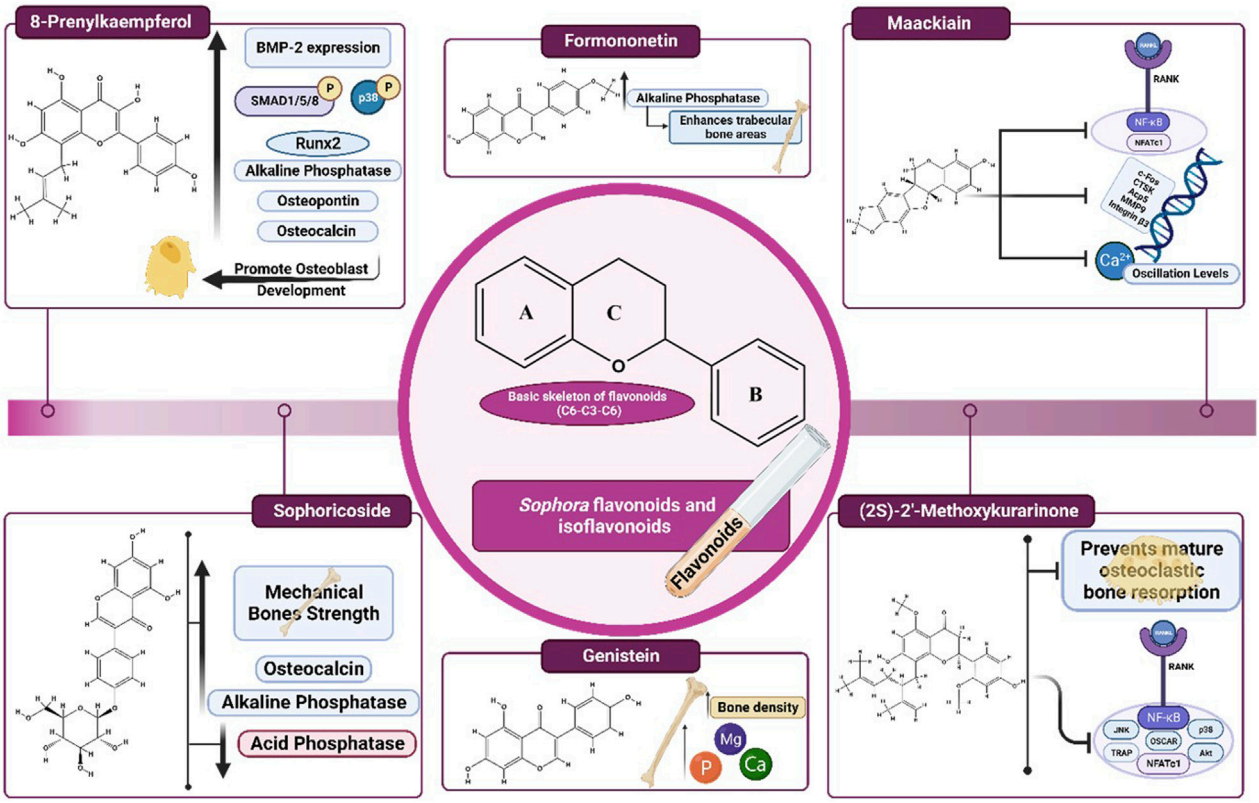


FIGURE 2
Sophora sp. flavonoids and isoflavonoids with underlying effects on bone health.

clinical studies are needed to evaluate the effect of this compound (Chiou et al., 2011b).

Formononetin (FORM) is a phytoestrogen isoflavone that demonstrated a wide range of physiological activities that benefit health *via* estrogen-dependent and independent pathways (Machado Dutra et al., 2021). FORM was isolated from *S. secundiflora* and *S. flavescens* (Jiang et al., 2019; Aly et al., 2021b). An *in vivo* study compared the therapeutic potency of three phytoestrogens, including genistein, daidzein, and FORM. In Sprague Dawley rats, they reported that FORM at doses of 1 and 10 mg/kg/day enhanced trabecular bone areas (TBAs) like genistein and 17□-estradiol (E2) by increasing the activity of ALP (Ha et al., 2010). The formononetin estrogenic efficacy may be attributed to equol the end product of the metabolic process of formononetin, which is characterized by a ketone group at C2 and a single bond between C1 and C8 that allows its higher binding affinity to ER. Also, the *in vitro* study utilizing ALP activity assays in Saos-2 cells showed that FORM significantly raised ALP activity to 33.0% ± 5.8% of the control group ($p < 0.05$) at a dosage of 1×10^{-4} mg/mL, indicating its potential to promote osteoblast proliferation (Ha et al., 2010). It's worth noting that FORM LD_{50} value equals to 103.6 mg/kg/BW (Pingale and Gupta, 2023).

Maackiain is a naturally occurring isoflavonoid derived from *S. flavescens* that exhibits several pharmacological properties, including anti-adipogenic, anti-allergic, anti-tumor, and immunostimulant activities (Huh et al., 2020; Liu et al., 2020; Mladenova et al., 2022). It showed activity in osteoclast-related conditions at *in vitro* study using concentrations of 5 μmol/L to 40 μmol/L. It disrupted the F-actin belt structures in mature osteoclasts and inhibited RANKL-stimulated protein levels and nuclear factor of activated T cells 1 (NFATc1) transcriptional activity. Moreover, it downregulated bone resorption-related genes, including c-Fos, CTSK, Acp5, MMP9, and integrin β3. It also inhibited Ca^{2+} oscillation levels, which suppressed gene expression related to osteoclasts (Liu et al., 2020) Table 1; Figure 2. The chemical structures of the flavonoids and isoflavonoids of *Sophora* sp. with potential effects on bone health are illustrated in Figure 3.

2.2 Alkaloids

Alkaloids are secondary metabolites that have been mainly found in plants. However, they have also been found in fungi and animals. This chemical class has more than 12,000 different structures (Schläger and Dräger, 2016). The essential characteristic of an alkaloid is the presence of a basic nitrogen atom (excluding nitrogen from an amide bond or peptide) in any molecular position (Gutiérrez-Grijalva et al., 2020). They are found in plants as powerful bioactive substances (Wang et al., 2022). They specifically have a variety of pharmacological properties, including anesthesia, cardioprotective, and anti-inflammatory effects. Morphine, strychnine, quinine, ephedrine, and nicotine are well-known alkaloids used in clinical practice (Heinrich et al.,

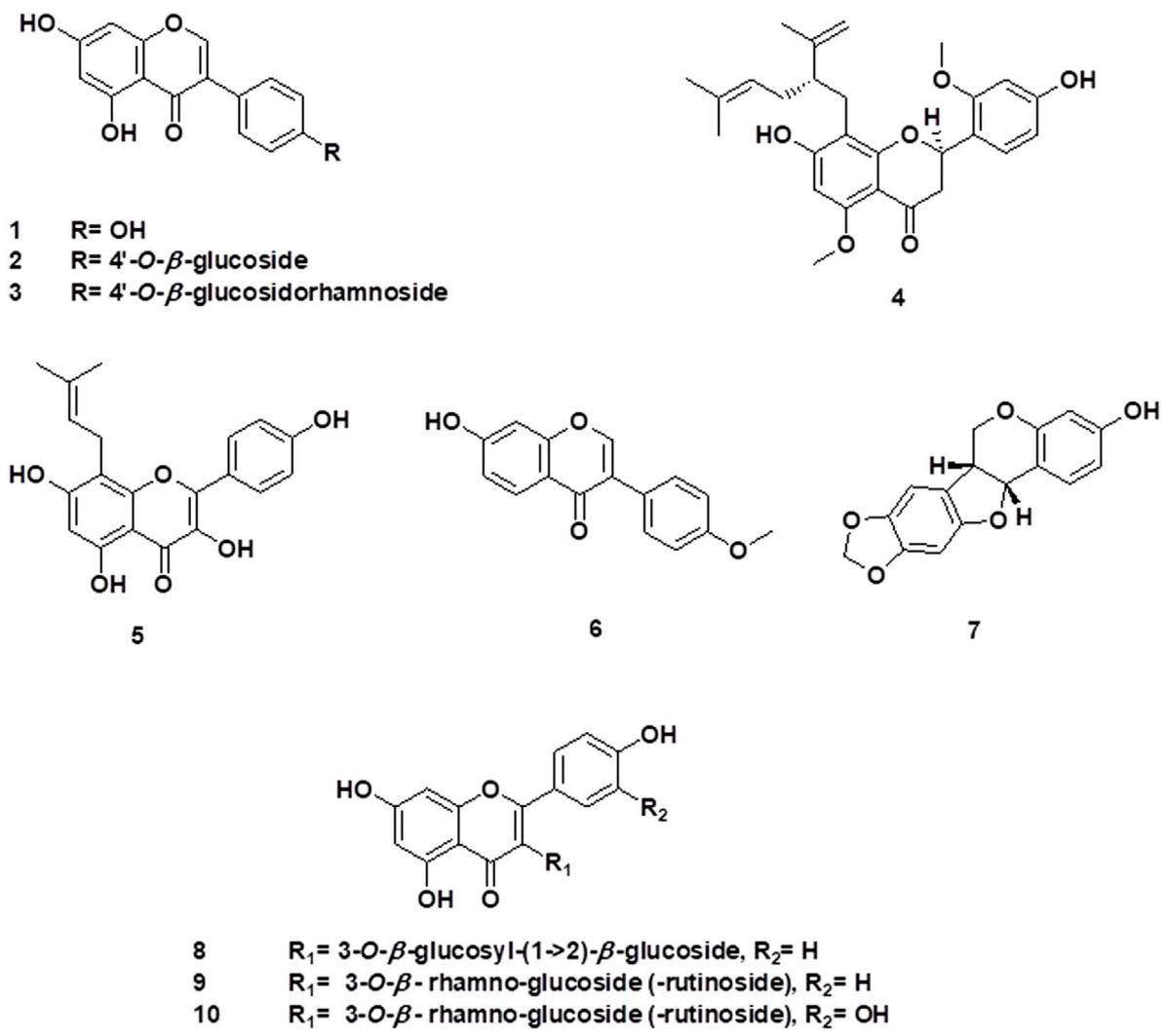


FIGURE 3
Chemical structures of the flavonoids and isoflavonoids of *Sophora* sp. with potential effects on bone health.

2021). They support the development of mesenchymal stem cells, boost osteoblast proliferation, encourage osteoblast autophagy, and inhibit the growth of osteoclasts. Alkaloids could control several signaling pathways, including blocking the interaction of tumor necrosis factor receptor-associated factor 6 (TRAF6) and receptor activator of nuclear factor κb (RANK), blocking the nuclear factor kappa B (NF-κB) pathway in osteoclasts, activating the p38 mitogen-activated protein kinases pathway in osteoblasts, and initiating the wingless and int-1 pathways in mesenchymal stem cells (Lin et al., 2022). Quinolizidine alkaloids are the main active compounds of *S. alopecuroides* (Zhang et al., 2022). They are generally synthesized through a biosynthetic pathway involving lysine amino acid (Bunsupa et al., 2012a) as represented by lupinine-type, cytisine-type, sparteine-type, and marine-type alkaloids (Wang et al., 2019). Previous investigations provided evidence indicating that the starting point in the production of quinolizidine alkaloids involves the decarboxylation of L-lysine into cadaverine, catalyzed by the enzyme lysine decarboxylase followed by cyclization (Golebiewski and Spenser, 1988). Various structurally related alkaloids can be produced by alterations in the main skeleton of quinolizidine alkaloids through selective processes such as dehydrogenation, oxygenation, or esterification (Bunsupa et al., 2012b). Lu et al. reported the impact of total alkaloids derived from *S. alopecuroides* on the growth of osteosarcoma cells. They found that the *S. alopecuroides* alkaloids at dose of 1.5, 3, and 4.5 g/kg were able to restrict the growth of human osteosarcoma OS732 cells by inhibiting their growth rate 18.4%, 27.4% and 52.8%, respectively using MTT assay (Lu et al., 2014).

Oxymatrine (OMT) is a quinolizidine alkaloid isolated from *Sophora* medicinal plants. It belongs to the matrine-type alkaloids. Previous research articles showed that OMT exhibited various pharmacological properties, including anti-inflammatory, anti-viral, anti-cancer, and anti-diabetic properties. It showed protective effects on the skin, bone, renal, vascular, gastrointestinal, liver, heart, and lung organs (Huan et al., 2023). OMT extracted from *S. flavescens* in an *in vitro* study using at concentrations of 0, 100, 200, and 400 μM suppressed sterol regulatory element-binding protein 2 (SREBP2) activation and the expression of downstream NFATc1 during

TABLE 2 ***Sophora*** **Alkaloids with potential effects on bone health.**

Compound name	*Sophora* species	Mechanism of action and efficiency	Study type	Model	Refs
Oxymatrine	*S. flavescens*	• Lowered ROS levels, which suppressed SREBP2 activation and downstream NFATc1 expression	*In vivo*	OVX mouse model	Jiang et al. (2021)
		• Suppressed RANKL-induced osteoclast-specific gene expression	*In vitro*	BMM cells	
		• Stopped OVX-induced osteoporosis			
Matrine	*S. flavescens, S. tonkinensis* var. *tonkinensis, S. alopecuroides*	• Inhibited TGF-β/Smad pathway-induced MSC migration and osteogenic differentiation is a possible treatment for HO.	*In vivo*	Heterotopic ossification (HO) mouse model	Mao et al. (2020)
			In vitro	BMCs	
		• Suppressed osteoclastogenesis and prevented ovariectomy-induced bone loss through reduced serum levels of TRAcp5b, TNF-α, and IL-6	*In vivo*	OVX mouse model	Chen et al. (2017)
		• Suppressed RANKL-induced activation of NF-κB, MAPK, and AKT pathways and NFATc1 expression in osteoclasts	*In vitro*	BMM cells and RAW264.7 cells	
			In vitro	BMM cells	
Sophoridine	*S. japonica*	• Inhibited the production of osteoclasts through the decrease in the level of the osteoclastogenesis marker CTX-1	*In vivo*	OVX mouse model	Zhao et al. (2017)
		• Reduced RANKL-induced activation of ERK and c-Fos and subsequently decreased the expression of NFATc1	*In vitro*	BMM cells	
Aloperine	*S. alopecuroides*	• Prevented the activity and formation of osteoclast that is mediated by RANKL.	*In vivo*	OVX mouse model	Hu et al. (2021)
		• Inhibited the expression of genes related to osteoclasts, such as MMP9, Ctsk, NFATc1, TRAcP, V-ATPase d2, and calcitonin receptor	*In vitro*	BMM cells	
		• Prevented the phosphorylation of P65, ERK, and JNK and IκBα degradation			
Total alkaloids of *S. alopecuroides* (TASA)	*S. alopecuroides*	• Inhibited the growth rate of human osteosarcoma OS732 cells	*In vitro*	Human osteosarcoma cell line OS732	Lu et al. (2014)

TABLE 3 ***Sophora*** **extracts with potential effects on bone health.**

Sophora species	Solvent used	Effect	Study type	Model	Ref
S. pachycarpa	Methanol extract/root	• Acted as a bone-formation stimulant	*In vitro*	Human adipose-derived mesenchymal stem cells	Mollazadeh et al. (2017)
		• Increased mineralization, ALP activity, and mRNA expression of BGLAP, RUNX2, SPP1, and COL1A1			
S. japonica	Ethanol extract/flower	• Downregulated NFATc1 and inhibited the differentiation of osteoclasts brought on by RANKL by inhibiting IκBα phosphorylation, which lowered the RANKL-mediated induction of the NF-κB pathway	*In vitro*	BMM cells	Kim et al. (2017)
S. japonica	40% water+60% EtOH extract/fruit	• Decreased drops in serum Ca and TBA and increased levels of Dpd	*In vivo*	OVX rat model	Shim et al. (2005)
S. japonica	Dichloromethane extract/fruit	• Showed the most potent pro-osteogenic activity as extract Increased early osteoblast marker ALP.	*In vitro*	Mesenchymal stem cells	Yoon et al. (2013)

osteoclastogenesis by lowering ROS levelsIt also suppressed RANKL-induced osteoclast-specific gene expression, which includes the c-fos, Nfatc1, Ctsk, Trap, Atp6v0d2, and Mmp9 genes. While OMT treatment suppressed the expression of these genes, RANKL upregulated them. OMT also stopped ovariectomy (OVX)-induced osteoporosis *in vivo* at dose of 10 mg/kg. Therefore, OMT may eventually prove to be a valuable medication for the treatment of osteoporosis (Jiang et al., 2021).

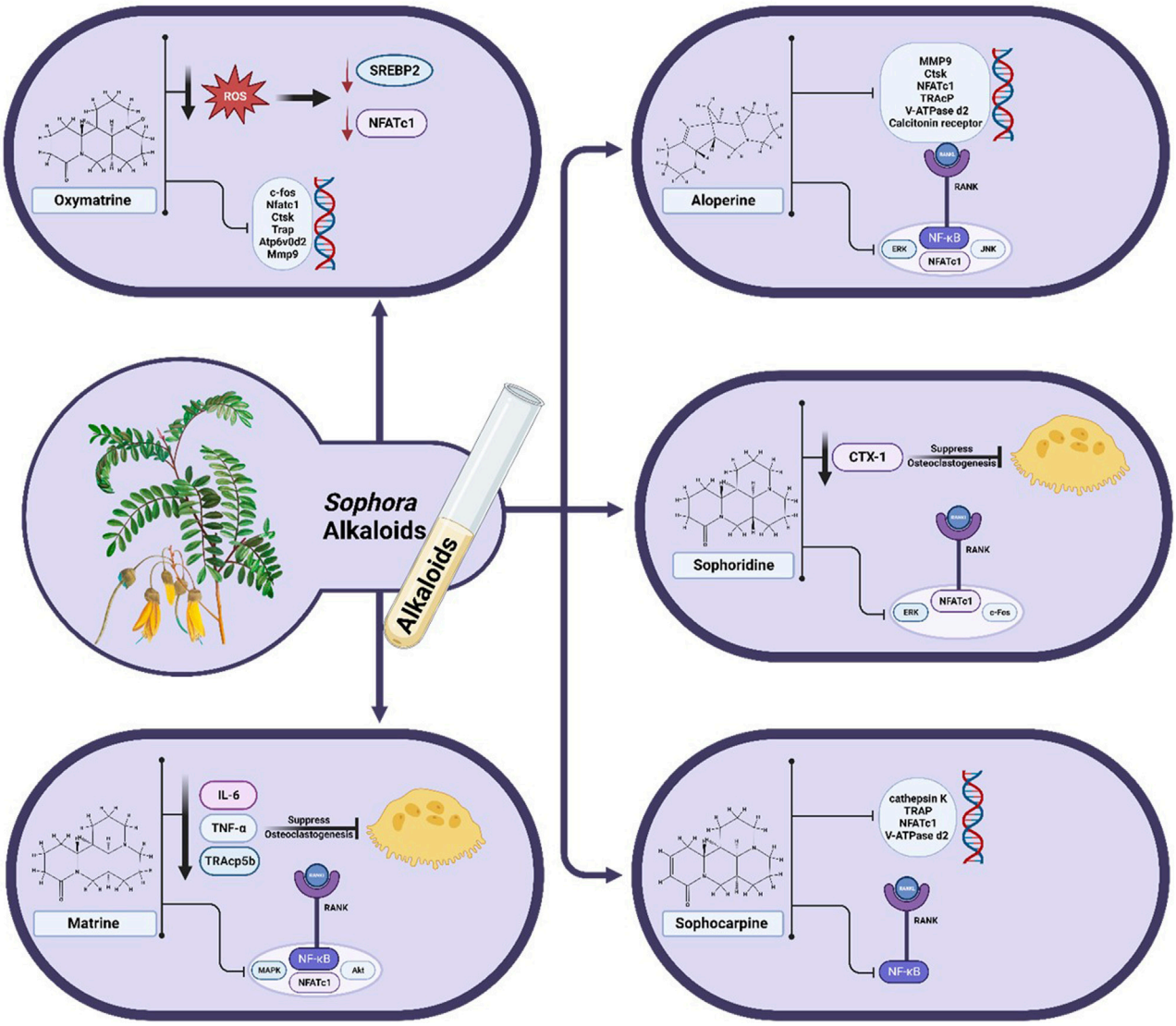


FIGURE 4
Sophora alkaloids with underlying effects on bone health.

Matrine is a quinolizidine alkaloid extracted from *S. alopecuroides*, *S. tonkinensis* var. *tonkinensis,* and *S. flavescens* (Dai et al., 2021; Liu N. et al., 2022). It showed various pharmacological effects, including anti-inflammatory, anti-tumor, and antiviral activities (Zhang et al., 2019; Luo et al., 2021; Liu J. et al., 2022). It demonstrated anti-fibrotic action by inhibiting the TGF-β/Smad pathway in liver, cardiac, and pancreatic fibrosis (Tan et al., 2023). Additionally, Mao et al. showed that inhibiting the TGF-β/Smad pathway is a possible treatment for heterotopic ossification (HO) by inducing mesenchymal stem cell (MSC) migration and osteogenic differentiation (Mao et al., 2020). Matrine may act as a novel osteoclastogenesis inhibitor at a dose of 150 mg/kg/d by suppressing numerous signaling pathways. It can suppress RANKL-induced activation of NF-κB, MAPK, and AKT pathways and NFATc1 expression in osteoclasts. As a result, it suppressed ERK, JNK, P38, and C-fos phosphorylation in the MAPK pathway, as well as inhibited AKT activation, resulting in lower expression of osteoclastogenesis-related markers such as MMP-9, TRAP, C-Src, and cathepsin K. It reduced serum levels of TRAcp5b, TNF-α, and IL-6, which suppressed osteoclastogenesis and prevented ovariectomy-induced bone loss. These effects indicated that matrine reduced bone loss in OVX mice by reducing osteoclastogenesis rather than increasing osteogenesis (Chen et al., 2017).

Another quinolizidine alkaloid is sophoridine, which is found in many traditional Chinese plants such as *S. davidi* var. *davidi*, *S. japonica* L., *S. flavescens* Alt., and *S. alopecuroides* L. (Tang et al., 2022). It showed various pharmacological actions such as anticancer, hepatoprotective, myocardial protective, antiviral, and anti-inflammatory effects (Wang et al., 2022). It exhibited antiosteoporosis and anti-osteoclastogenic effects *in vivo* at a dose of 15 mg/kg. Its anti-osteoporosis was achieved through the inhibition of osteoclast production and the suppression of anti-osteoclastogenic effect by reducing RANKL-induced activation of

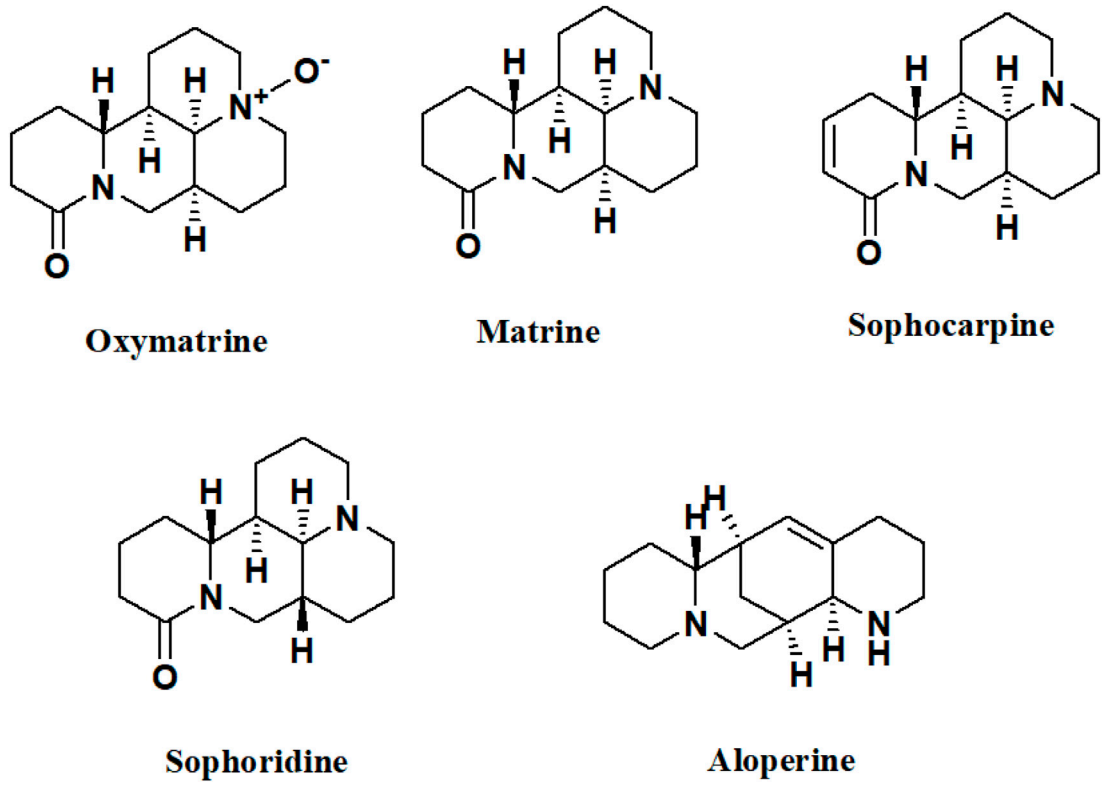


FIGURE 5
Chemical structures of the alkaloids of *Sophora* sp. with potential effects on bone health.

ERK and c-Fos and subsequently decreasing the expression of NFATc1, the most crucial factor in controlling osteoclastogenesis. It also reduced the level of the osteoclastogenesis marker CTX-1 rather than the osteogenesis marker OCN, indicating that sophoridine only inhibited osteoclastogenesis to tackle osteoporosis (Zhao et al., 2017).

Aloperine is a quinolizidine alkaloid found in the leaves and seeds of the medicinal plant *S. alopecuroides* L. (Zhou et al., 2020). Due to its potent anti-inflammatory, antioxidant, antibacterial, and antiviral effects, it has been used as a herbal medicine in China for centuries. It was established that aloperine is a potent therapeutic agent for various pathological diseases, including viral infections, cardiovascular and inflammatory disorders, and cancer (Tahir et al., 2022). Without influencing the activity of BMMs, In an *in vitro* investigation, aloperine was found to inhibit osteoclast activity and formation induced by RANKL *via* decreasing the ERK, JNK, and NF-κB pathways. This effect was observed at various concentrations of 10, 20, 40, and 50 μM. Additionally, it inhibited the expression of genes related to osteoclasts, such as matrix metallopeptidase 9 (MMP9), cathepsin K (Ctsk), NFATc1, tartrate-resistant acid phosphatase (TRAcP), V-ATPase d2, and calcitonin receptor. It prevented the phosphorylation of P65, ERK, and JNK and IκBα degradation. At a dosage of 30 mg/kg *in vivo*, it effectively decreased osteoclast activity and mitigated bone loss in OVX mice (Hu et al., 2021).

Alkaloids from *S. flavescens* (ASF) showed potent anti-inflammatory and proliferative effects on *Staphylococcus aureus* infected rat calvarial osteoblasts (ROBs) treated or untreated with vancomycin through increased viability of ROBs. These results might be obtained by controlling the mRNA and protein expression of BMP2, Runx2, OPG, and RANKL, reducing the secretion of the inflammatory factor TNF-α, and boosting ALP activity. ASF also reduced TRAP activity and osteoclast viability. As a result, when combined with an antibiotic, ASF might be a potential supplementary herbal treatment for chronic osteomyelitis (Wang et al., 2018), as depicted in Table 2 and Figure 4.

Figure 5 illustrates the chemical structures of the alkaloids of *Sophora* sp. with potential effects on bone health.

2.3 *Sophora* extracts

Sophora pachycarpa root extract (SPRE), acts as a stimulant for bone-formation in human adipose-derived mesenchymal stem cells. *In vitro*, SPRE demonstrated a significant increase in mineralization, ALP activity, and mRNA expression of bone gamma-carboxyglutamate protein (BGLAP), RUNX2, secreted phosphoprotein 1 (SPP1), and collagen type I alpha 1 (COL1A1) at different concentrations of 0.1, 1, 5, and 10 μg/mL (Mollazadeh et al., 2017).

The flowers and buds of *S. japonica* are called Sophorae Flos (SF) (Shi et al., 2023). The SF showed anti-obesity, anti-allergic, antiproliferative, and anti-inflammatory effects. Kim et al. found that SF extract showed inhibitory effects on IκBα phosphorylation *in vitro*, this resulted in a reduction of the NF-κB pathway activation induced by RANKL at different concentrations (0, 50, 100, 200 μg/mL). As a result,

NFATc1 was downregulated, and the differentiation of osteoclasts brought on by RANKL was inhibited. These results demonstrated that SFE might be a potent candidate for managing inflammatory bone disorders, including osteoporosis, rheumatoid arthritis, and periodontitis (Kim et al., 2017).

The administration of *Sophorae fructus* extract at a dose of 0.556 g/kg/day in OVX rats decreased serum Ca and TBA and increased the levels of Dpd. These findings showed that this extract efficiently prevented bone loss and suggested that *Sophorae fructus* might be developed as a potential agent in preventing and treating osteoporosis (Shim et al., 2005).

The mature fruit of *S. japonica* L. was extracted using ethanol, hexane, dichloromethane (DCM), ethyl acetate, and butanol, which were investigated for their effects on the differentiation of C3H10T1/2 cells into osteoblasts at 10, 25, 50, and 100 μg/mL. Among the studied extracts, the *in vitro* study revealed that the DCM extracts showed the most potent pro-osteogenic activity. The DCM extract significantly increased early osteoblast marker ALP activity compared with the tested extracts. The DCM fractions contained significant quantities of genistein. The expression of estrogen target genes was also altered similarly to the effect of genistein and DCM fractions, and both substances were active in transfection tests that assessed estrogen agonistic activity (Yoon et al., 2013). The impact of *Sophora* extracts on bone health is presented in Table 3.

3 Conclusion

This review focused on the genus *Sophora* derived secondary metabolites and extracts in managing bone diseases, especially osteoporosis. We highlighted the reported flavonoids, isoflavonoids, and alkaloids from different *Sophora* species with potential roles in bone repair and maintenance of bone health. We explored their mechanisms of action that would potentially demonstrate their clinical efficacy. The mechanism of *Sophora* flavonoids and isoflavonoids is based on enhancing the mechanical strength of bones and a significant increase in osteogenic biochemical markers such as serum ALP, OCN levels, and BMP-2 expression. *Sophora* species increased bone mineral components such as calcium, phosphorus, and magnesium. On the other hand, the reduction of Ca^{2+} oscillation levels further suppressed the expression of genes associated with osteoclasts. *Sophora* alkaloids facilitated the growth of mesenchymal stem cells, enhanced the proliferation of osteoblasts, promoted osteoblast autophagy, and hindered the proliferation of osteoclasts. These investigations can potentially drive research toward developing new bone health medications derived from the *Sophora* genus. Furthermore, synthesizing more potent derivatives and investigating their mechanisms of action, exploring their pharmacokinetics and clinical efficiency. There is a lack of clinical trials in the existing literature that investigate the effectiveness and pharmacological effects of *Sophora* in alleviating osteoporosis. A comprehensive research framework, including clinical trials and preclinical evaluations, is essential for validating the therapeutic efficacy of *Sophora* extracts and isolated compounds in the management of osteoporosis that can derive research in producing more potent therapeutic agents tackling bone diseases.

Author contributions

SA: Conceptualization, Data curation, Resources, Visualization, Writing–original draft. AE: Visualization, Investigation, Resources, Writing–original draft. ME-S: Project administration, Supervision, Validation, Writing–review and editing. T-LH: Project administration, Supervision, Validation, Writing–review and editing.

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Glossary

8-PK	8-prenylkaempferol
ALP	alkaline phosphatase
ASF	Alkaloids of *S. Flavescens*
BGLAP	bone gamma-carboxyglutamate protein
BMD	bone mineral density
Bmms	bone marrow macrophages
BMP	bone morphogenetic protein
COL1A1	collagen type I alpha 1
Coll 1	type 1 collagen
Ctsk	cathepsin K
DCM	Dichloromethane
FORM	Formononetin
FS	Fructus Sophorae
IDD	intervertebral disc degeneration
MK	(2S)-2′-methoxykurarinone
MMP9	Matrix metallopeptidase 9
MSC	Mesenchymal Stem Cell
Nfatc1	nuclear factor of activated T cells 1
NF-κb	nuclear factor kappa B
OCN	osteocalcin
OMT	Oxymatrine
OPN	osteopontin
Osx	osterix
OVX	ovariectomy/ovariectomized
PMOP	postmenopausal osteoporosis
RANK	receptor activator of nuclear factor- κβ
RANKL	receptor activator of nuclear factor-κb ligand
Robs	Rat Calvarial Osteoblasts
Runx2	runt-related transcription factor 2
SF	Sophorae Flos
SFE	Sophorae Flos Extract
SPP1	Secreted Phosphoprotein 1
SPRE	*Sophora pachycarpa* root extract
SREBP2	suppresses sterol regulatory element-binding protein 2
Tbas	trabecular bone areas
Tracp	tartrate resistant acid phosphatase
TRAF6	tumor necrosis factor receptor-associated factor 6
WNT	Wingless-INT