



Exploring the Osteoprotective Mechanisms of *Sambucus Williamsii* Hance: A Comprehensive Narrative Review

Amir Hossein Jahanbani¹, Mohammad Safakhalaj¹, Mohsen Pourebrahimi¹, Zahra Saeidi Pakdel², Reza Aletaha^{3,4*} 

¹Department of Epidemiology & Biostatistics, Kashan University of Medical Sciences, Kashan, Iran

²Department of Analytical Chemistry, Faculty of Pharmacy, Istanbul Aydin University, Istanbul 34295, Türkiye

³Neurosciences Research Center, Aging Research Institute, Tabriz University of Medical Sciences, Tabriz, Iran

⁴Social Determinants of Health Research Center, Department of Community Medicine, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran

Article History:

Received: November 30, 2025

Revised: December 3, 2025

Accepted: December 12, 2025

ePublished: December 29, 2025

*Corresponding Author:

Reza Aletaha,

Email: Raletaha77@gmail.com

Abstract

Background: Osteoporosis, marked by reduced bone density and increased fracture risk, remains a serious public health challenge. *Sambucus williamsii* Hance (SWH), a traditional Chinese medicine, has been traditionally used for bone disorders and may represent a natural alternative to pharmacological therapies. Accordingly, this review evaluated the therapeutic potential and mechanisms of SWH extracts in osteoporosis management.

Methods: A narrative review was conducted, and PubMed, Scopus, and Web of Science databases were searched for studies investigating SWH and osteoporosis in preclinical and clinical environments, focusing on populations at risk for osteoporosis, including postmenopausal and diabetic individuals.

Outcome Measures: The primary outcomes included the effects of SWH extracts on bone formation and resorption, molecular mechanisms involved, and impacts on metabolic risk factors affecting bone health.

Results: In general, SWH extracts were found to promote bone formation while inhibiting bone loss through genomic and non-genomic estrogen receptor pathways, involving mitogen-activated protein kinase and cyclic guanosine monophosphate-mediated protein kinase G type-2 signaling. Additional benefits on dyslipidemia, insulin resistance, and inflammation were also observed, potentially contributing to improved bone health in high-risk populations. SWH may offer safety and efficacy advantages over conventional estrogen-based therapies.

Conclusion: SWH appears to be a promising natural candidate for osteoporosis treatment, with multi-faceted benefits and a favorable safety profile. Nonetheless, further clinical research is needed to confirm these findings and define its role in clinical practices.

Keywords: *Sambucus Williamsii* Hance, SWH, Osteoporosis, Narrative review

Introduction

Reduced bone density and changed bone structure are the hallmarks of osteoporosis, which is a disorder of the skeletal system that increases the risk of fractures, especially in the wrist, spine, and hip.¹ One important contributing factor to the development of osteoporosis is the gonadal function decline that happens with age and post-menopause. Osteoporosis is becoming an increasingly important global health concern as the world's population ages.² Fractures and the resulting medical expenses are examples of direct repercussions. In addition, poorer productivity and a worse standard of living are examples of indirect implications. Moreover, osteoporosis is becoming more and more common worldwide, has a major influence on people's health, and requires a thorough resource to bring information together and provide guidance for its management and prevention. Currently, the pharmacological interventions for the treatment of osteoporosis include calcitonin,

recombinant human parathyroid hormone, selective estrogen receptor modulators, estrogen, bisphosphonates, and the monoclonal antibody receptor activator of nuclear factor-kappa- β ligand (RANKL).^{3,4} In addition, estrogen replacement therapy was once a commonly used strategy for the prevention and treatment of postmenopausal osteoporosis. However, new research suggests that estrogen replacement therapy is associated with an increased risk of endometrial, breast, and ovarian malignancies.⁵⁻⁸ A safer and more palatable option for treating osteoporosis might be provided by the traditional Chinese medicine, which has a long history of clinical applications.⁹ *Sambucus williamsii* Hance (SWH) is a Chinese traditional plant that is also referred to as JieGuMu, which may be literally translated as "the wood which links bones." In the Chinese context, for many centuries, it has been used in the treatment of various ailments affecting the joints and bones, such as gout, rheumatoid arthritis, bone fractures, traumas, and Kaschin-Beck disease.^{10,11} Moreover, it



serves as a powerful tool for assessing the therapeutic effects of herbal treatments and elucidating the underlying mechanisms that drive these effects.¹²⁻¹⁴ Accordingly, this research primarily aims to conduct a comprehensive investigation of the potential advantages and the therapeutic role of SWH in osteoporosis management.

Methods

Search Strategy and Eligibility Criteria

PubMed, Scopus, and the Web of Science databases were searched, without any time or language constraints, up to December 28, 2024. The applied search terms included a comprehensive combination of terms related to SWH and osteoporosis as follows:

“Sambucus Williamsii Hance” OR “SWH” OR “North China red elder” OR “Jiegumu”) AND (“Osteoporosis” OR “Osteoporoses” OR “Bone Loss”)

The inclusion criteria used for the review included studies reporting the use of SWH regardless of the study design and population and studies written in English language. On the other hand, the exclusion criteria were unpublished manuscripts, conference abstracts, editorials, or trial protocols and non-English language studies.

Study Selection

Records from the search were imported into Endnote software (version 21). Two blinded reviewers screened each paper using the titles and abstracts to identify articles to be retrieved for a full review. The reviewers assessed the retrieved articles for inclusion in the final review and subsequent data extraction. Further, any possible disagreements on study selection and data extraction were resolved by consensus between the reviewers.

Data Collection Process

Data extracted from each article included first author's name, year of publication, country of the study, study design, objectives of the study, intervention and control definitions, total sample size, group sizes, outcome measures, main results, and conclusions/implications.

Sambucus: Biological Effects and Bioavailability

North-eastern China is home to the shrub or small tree known as *Sambucus williamsii*, which may grow up to six meters in height. As the branches mature, they acquire a reddish-brown coloration and have narrowly elliptical lenticels on their outer layer. SWH, often referred to as Jiegumu in the traditional Chinese medicine, is used for the therapeutic management of bone and joint disorders. Phenolic acids, lignans, and terpenoids are the main bioactive components of SWH. Moreover, there are trace amounts of minerals, amino acids, essential oils, and natural pigments.¹⁵

An analysis of the n-butanol extract obtained from the fruits of SWH revealed seventeen chemicals, including fifteen previously known compounds and two previously unidentified phenylethanoid glycosides. Extensive spectroscopic data was the primary method used to

determine the structures of these new compounds, which included two-dimensional nuclear magnetic resonance. Additionally, in primary grown mouse liver cells, the n-butanol extract from the fruits of SWH demonstrated a protective effect against D-galactosamine-induced toxicity. Additionally, liver-protective qualities were compounds 13, 16, and 17.¹⁶

Sambucus has a protective effect on cells that cause breast cancer. The extract obtained from *Sambucus ebulus* exhibited a substantial decrease in cellular growth and viability. Normal breast cells are not threatened by this extract, but it is quite successful in identifying and destroying malignant ones. According to an analysis of gene expression linked to the cell cycle and apoptosis, Bax, Bak, P53, and c-MYC levels are significantly increased by fraction 4 of the *S. ebulus* extract. Similarly, living species and experimental settings have both shown this effect of the *S. ebulus* extract. Therefore, the extract from *S. ebulus* displays promise as a safe herbal treatment for eliminating breast cancer cells without endangering healthy host cells.¹⁷ Xiao et al successfully extracted and characterized two recently discovered phenylpropanoids (i.e., samwirin and samwiphenol) with a previously unidentified sesquiterpenoid referred to as 2 β ,4 β ,10 α -trihydroxy-1 α H,5 β H-guaia-6-ene. They assessed the influence of these chemicals on the proliferation of osteoblast-like UMR-106 cells in a controlled laboratory environment. Compounds 1, 4–9 showed a considerable increase in cell proliferation. Specifically, it was shown that compounds 5, 6, and 8 demonstrated separate increases in the number of osteoblastic cells by 24.3%, 25.2%, and 29.1% at concentrations of 10(-10) M, 10(-10) M, and 10(-8) M, respectively.¹⁸

Many phytochemicals found in SWH, such as (+)-pinoresinol, lariciresinol, and (+)-medioresinol, have antibacterial qualities against pathogenic microbes. A phytochemical called OLI9G has been isolated from SWH, and its antifungal characteristics and mode of action have been investigated. The antifungal actions of OLI9G are manifested via its ability to damage the integrity of the cell membrane. In addition, this chemical has promising prospects for the development of innovative antifungal therapies.¹⁹

The administration of the lignan-rich fraction (SWCA), recognized for its anti-osteoporotic capabilities, by oral route in ovariectomized (OVX) rats has various advantages, including the amelioration of dyslipidemia, improvement of hepatic function, protection against glucose intolerance and insulin resistance, mitigation of systemic inflammation, and reinforcement of the intestinal barrier. It further facilitates an increased abundance of Actinobacteria and reinstates the microbial makeup.²⁰

Sambucus and Osteoporosis: Therapeutic and Mechanistic Aspects

SWH extracts can reduce the excretion of calcium in the urine in a dose-dependent way. In addition, they induce an increase in blood calcium levels and improve the mineral

density of both tibial and femoral bones. Furthermore, they have beneficial effects on the microarchitecture of trabecular bone in mice that have had OVX. Additionally, SWH extract therapy reduces the elevated levels of serum osteocalcin, serum alkaline phosphatase (ALP), and urine deoxypyridinoline caused by OVX. In addition to suppressing the production of core binding factor- $\alpha 1$ messenger ribonucleic acid (mRNA) and cathepsin K mRNA that are increased by ovariectomy, SWH also increases the ratio of osteoprotegerin (OPG)/RANKL mRNA expression in the tibia. The results of in vitro investigations indicated that SWH has a considerable effect on reducing the population of tartrate resistant acid phosphatase-positive cells in RANKL-induced RAW 264.7 cells. As a result of blocking bone resorption and encouraging bone formation, SWH is useful in improving the quality of bones.²¹

SWH stands out among the prospective treatments for postmenopausal osteoporosis. The inhibitory effects of the chloroform and ethyl acetate fractions of SWH on osteoclastogenesis have been observed via the regulation of OPG and RANKL mRNA expression in osteoblastic UMR-106 cells. The mentioned fractions can enhance OPG mRNA levels while simultaneously reducing the production of RANKL mRNA. This leads to a proportional increase in the OPG/RANKL mRNA ratio, with the magnitude of the effect being dependent on the administered dosage. While there may be a reduction in osteoclast development, the use of SWH therapy successfully reduces the increase in bone turnover brought on by OVX. Furthermore, proliferation and ALP activities are markedly stimulated by vanillic acid, which is a phenolic acid obtained from the bioactive fraction of SWH. Additionally, it causes significant alterations in UMR-106 cells' mRNA expression of genes linked to osteoblast activities and osteoclastogenesis. Unlike the conventional method, vanillic acid, identified as a bioactive component in SWH, activates osteoblast-like cells via a non-genomic estrogen receptor signaling pathway.^{22,23}

Lignans are probably the main bioactive components of SWC s.²⁴ Compounds 2–9, which have been characterized as lignans derived from the anti-osteoporotic fraction of SWH (i.e., compounds 2, 3, 4, 5, and 7), exhibit a remarkable enhancement in cellular proliferation.²⁵

The administration of SWCA demonstrated significant efficacy in attenuating bone loss and reducing serum serotonin levels, which had a negative association with bone mineral density (BMD) in the rat model. Moreover, it suppressed the expression of the tryptophan hydroxylase 1 (TPH-1) protein in the colon and the genetic and protein expression of activating transcription factor 4 and forkhead box protein O1 in the femur of OVX rats. Following SWCA therapy, the percentage of Antinobacteria increased, and various BMD-associated genera were affected. This suggests that lignans may have bone-protective effects via acting on serotonin, highlighting that lignans have potential as a viable source of TPH-1 inhibitors.²⁶

In OVX rats, SWRH efficiently counteracts changes in 26 metabolites brought on by an estrogen shortage. Lipids, amino acids, tryptophan metabolism, and the antioxidant system are all linked to these alterations. After undergoing SWR therapy, a notable rise was observed in the serum concentrations of superoxide dismutase and catalase. Conversely, there was a decline in serotonin levels in cells that expressed high levels of TPH-1, as found in RBL-2H3 cells obtained from rats.²⁷

The effect of PPD is neutralized when it is co-incubated with ICI182,780 or U0126. Runx2, ALP, and osteocalcin mRNA expressions are stimulated by PPD, which also increases the ratio of OPG/RANKL. It is noteworthy that PPD does not display binding affinity toward either estrogen receptors (ER) ER α or ER β or does not induce estrogen response element-luciferase activity via ER activation. In contrast, it elicits the phosphorylation of extracellular regulate kinases, a phenomenon that is completely abolished by U0126. Moreover, it evokes the phosphorylation of ER α at serine 118. Briefly, PPD, a bioactive substance found in SWH, causes osteoblast-like cells to react similarly to estrogen. Estrogen response elements initiate a fast non-genomic ER signaling mechanism via a ligand-independent route that is aided by the mitogen-activated protein kinase.²⁸

Diabetes-related osteopenia mostly arises from impaired bone growth resulting from elevated blood glucose levels. When MC3T3-E1 cells are exposed to high glucose, they exhibit heightened oxidative stress (OS) primarily because pro-oxidant gene expression is upregulated and antioxidant gene expression is downregulated. On the other hand, the SWH extract reduces OS via controlling genes such as *NADPH oxidase-4* and associated thioredoxin genes by increasing the amounts of the cyclic guanosine monophosphate (cGMP)-mediated protein kinase G type-2 (PKG2) and activating the formation of cGMP. Oral administration of the SWH extract reduces OS while promoting osteogenesis, helping to preserve bone homeostasis in mice with type 1 diabetic mellitus. It should be noted that the SWH extract confers its bone-protective properties on MC3T3-E1 cells exposed to high glucose and mice with hyperglycemia-induced osteopenia through activating the cGMP/PKG2 signaling pathway. As a result, pro-oxidant gene expression declines while antioxidant gene expression represents an increase. Overall, excessive blood sugar levels may cause osteopenia, while the SWH extract protects against that the degradation of bones by reducing OS via the cGMP/PKG signaling pathway. This observation implies that it has the potential to be a favorable treatment strategy for managing diabetes-related osteopenia.²⁹ Table 1 provides a summary of relevant studies.

Conclusion

In summary, the comprehensive review of the multifaceted biological effects of SWH underscores its considerable potential in the management of osteoporosis. The obtained data indicated that compounds from SWH

Table 1. Study Characteristics

Dose	Route	Target(s)	Finding(s)	Model	Animal Type	Cell Line	Duration	Reference
SWH [†] : 30 or 60 mg/100 g/day	Oral	OPG and RANKL mRNA	Increased serum Ca levels; decreased urinary Ca excretion; downregulated serum ALP, serum osteocalcin, and urinary deoxypyridinoline; increased stiffness of femur; BMD in tibia significantly increased.	In vivo and in vitro	OVX Sprague-Dawley SPF virgin female rats	UMR-106 cells	3 months	21
SWH: 200, 500, 1,000 mg/kg/day	Oral	Cbfa1 mRNA; cathepsin K mRNA; OPG and RANKL mRNA	Decreased urinary Ca excretion, increased serum Ca levels, increased tibial BMD; improved trabecular bone microarchitecture	In vivo and in vitro	Virgin female C57BL/6J mice	RAW 264.7 cells	12 weeks	22
Vanillic Acid (VA) [‡] : 10 ⁻¹² to 10 ⁻⁷ M	-	Runx2, osteocalcin, OPG and RANKL mRNA	Exerted estrogen-like activities; stimulated differentiation and Ca deposition in MC3T3-E1 and BMSC cells; promoted osteoblastic functions in bone cells	In vitro	-	MC3T3-E1 cells, UMR-106 cells, and BMSC	18 days	23
SWH: 1.0 mg/g body weight/day; SWA [‡] : 0.57 mg/g/day; SWB ^{††} : 0.128 mg/g/day; SWC [‡] : 0.189 mg/g/day	Oral	ALP	Suppressed estrogen deficiency-induced weight gain; restored BMD at femur and tibia; improved bone microstructure; increased stiffness of tibial mid-shaft; enhanced cell proliferation and differentiation in vitro	In vivo and in vitro	Virgin C57BL/6J SPF female mice	UMR-106 cells	3 months (in vivo); 24-48 hours (in vitro)	24
SWCA ^{‡‡} : 140 and 280 mg/kg/day	Oral	Osteocalcin; C-terminal telopeptide fragments of type I collagen; ALP; 5-HT; ATF4; FOXO1; TPH-1 protein	Improved bone properties; prevented trabecular BMD reduction and bone microarchitectural damage; reduced serum 5-HT; altered gut microbiota	In vivo	OVX Sprague-Dawley female rats	-	10 weeks	26
PPD [‡] : 10 ⁻¹² to 10 ⁻⁷ M	-	ALP, Runx2, osteocalcin, OPG, RANKL, MAPK signaling, and ERK	Increased cell proliferation; stimulated calcium deposition in BMSC; altered mesenchymal stem cell differentiation into osteoblasts; exerted estrogenic effects by inducing gene expression involved in osteoblastic differentiation	In vitro	-	UMR-106 cells, MC3T3-E1 cells, BMSC	18 days	28
SWH: 340 and 680 mg/kg/day (in vivo); 30, 60, 90 µg/mL (in vitro)	Oral	Runx2, Sp7 protein, JNK, P38, cGMP, PKG1 and PKG2 mRNA, Txn1 and Nox4 mRNA	Restored osteogenic differentiation; reduced oxidative stress (lowered MDA levels); improved bone microarchitecture and bone strength	In vivo and in vitro	Streptozotocin-induced type 1 diabetic C57BL/6J female mice	MC3T3-E1 cells	8 weeks (in vivo); 24-48 hours (in vitro)	29

Note. SWH: Sambucus williamsii Hance; OPG: Osteoprotegerin; RANKL: Receptor activator of nuclear factor kappa-β ligand; Ca: Calcium; ALP: Alkaline phosphatase; BMD: Bone mineral density; OVX: Ovariectomized; Cbfa1: Core binding factor-α1; Runx2: Runt-related transcription factor 2; BMSC: Bone mesenchymal stem cells; 5-HT: 5-Hydroxytryptamine; ATF4: Activating transcription factor 4; FOXO1: Forkhead box protein O1; TPH-1: Tryptophan hydroxylase 1; MAPK: Mitogen-activated protein kinase; ERK: Extracellular signal-regulated kinases; P: Phosphorus; M: Molar; Sp7: Specificity protein-7; JNK: Jun N-terminal kinase; cGMP: Cyclic guanosine monophosphate; PKG: Cyclic GMP-dependent protein kinase; Txn1: Antioxidant gene thioredoxin; Nox4: NADPH oxidase 4.
□ A bioactive fraction of SWH
† Water eluate SWH
†† 30% ethanol eluate SWH
‡ 50% and 95% ethanol eluates SWH
‡‡ A purified fraction from SWC
¥ A bioactive ingredient in SWH

not only facilitate bone formation but also reduce bone resorption through a variety of pathways. Additionally, the osteoprotective properties of these extracts are not limited to their impacts on BMD and microarchitecture. It was demonstrated that SWH compounds can alleviate systemic metabolic disturbances, including dyslipidemia, glucose intolerance, and inflammation, as well as reducing OS. These pleiotropic actions not only contribute to the maintenance of bone homeostasis in a variety of pathological conditions (e.g., postmenopausal osteoporosis and diabetes-associated osteopenia) but also indicate a potential for a broader improvement in overall metabolic dysfunction.

It is crucial to remain aware of the current constraints in translating preclinical insights into clinical practices,

despite these promising findings. Although in vitro and animal studies provide substantial evidence of the efficacy of SWH-derived compounds, additional clinical trials are required to verify safety profiles, optimal dosages, and long-term benefits in human populations. In addition, future research should concentrate on elucidating the precise molecular mechanisms that underlie these effects and investigating potential synergies with current pharmacological treatments.

Overall, SWH is a strong contender for safer and more efficient osteoporosis treatment. This natural remedy is promising and warrants further clinical investigations due to its capacity to regulate critical biochemical pathways that are involved in bone remodeling, as well as its ancillary effects on metabolic health. Therefore, this narrative

review established a strong foundation for future research designed to combine traditional botanical knowledge with contemporary therapeutic strategies in order to address the global epidemic of osteoporotic diseases.

Authors' Contribution

Conceptualization: Reza Aletaha, Amir Hossein Jahanbani.

Data Curation: Reza Aletaha, Mohammad Safakhalaj

Formal Analysis: Reza Aletaha, Mohsen Pourebrahimi, Amir Hossein Jahanbani

Investigation: Reza Aletaha, Mohammad Safakhalaj

Data Availability Statement

The study data are available upon a reasonable request from the corresponding author.

Competing Interests

The authors declare that they have no competing interests.

Consent for Publication

Not applicable.

Ethical Approval

Not applicable.

Funding

This study received no financial support.

References

- Lock CA, Lecouturier J, Mason JM, Dickinson HO. Lifestyle interventions to prevent osteoporotic fractures: a systematic review. *Osteoporos Int* 2006;17(1):20–8. doi:10.1007/s00198-005-1942-0
- Notelovitz M. Estrogen therapy and osteoporosis: principles & practice. *Am J Med Sci* 1997;313(1):2–12. doi:10.1097/00000441-199701000-00002
- Ponnappakkam T, Katikaneni R, Sakon J, Stratford R, Gensure RC. Treating osteoporosis by targeting parathyroid hormone to bone. *Drug Discov Today* 2014;19(3):204–8. doi:10.1016/j.drudis.2013.07.015
- Lessler J, Reich NG, Cummings DA, Nair HP, Jordan HT, Thompson N. Outbreak of 2009 pandemic influenza A (H1N1) at a New York City school. *N Engl J Med* 2009;361(27):2628–36. doi:10.1056/NEJMoa0906089
- Davison S, Davis SR. Hormone replacement therapy: current controversies. *Clin Endocrinol (Oxf)* 2003;58(3):249–61. doi:10.1046/j.1365-2265.2003.01774.x
- Beral V, Banks E, Reeves G, Appleby P. Use of HRT and the subsequent risk of cancer. *J Epidemiol Biostat* 1999;4(3):191–210; discussion –5.
- Persson I, Weiderpass E, Bergkvist L, Bergström R, Schairer C. Risks of breast and endometrial cancer after estrogen and estrogen-progestin replacement. *Cancer Causes Control* 1999;10(4):253–60. doi:10.1023/a:1008909128110
- Rodriguez C, Calle EE, Coates RJ, Miracle-McMahill HL, Thun MJ, Heath CW, Jr. Estrogen replacement therapy and fatal ovarian cancer. *Am J Epidemiol* 1995;141(9):828–35. doi:10.1093/oxfordjournals.aje.a117518
- Xiao HH, Sham TT, Chan CO, Li MH, Chen X, Wu QC, et al. A Metabolomics Study on the Bone Protective Effects of a Lignan-Rich Fraction From *Sambucus Williamsii* Ramulus in Aged Rats. *Front Pharmacol* 2018;9:932. doi:10.3389/fphar.2018.00932
- Song L. Chinese Bencao. Shanghai: Shanghai Science and Technology Press Original Edition, Chinese Bencao[Google Scholar]. 2000.
- Xiao HH, Zhang Y, Cooper R, Yao XS, Wong MS. Phytochemicals and potential health effects of *Sambucus williamsii* Hance (Jiegumu). *Chin Med* 2016;11:36. doi:10.1186/s13020-016-0106-9
- Chu HY, Zhang A, Han Y, Wang X-j. Metabolomics and Its Potential in Drug Discovery and Development From TCM. *Traditional Chinese Medicine* 2015;1:26–32.
- Hu C, Xu G. Metabolomics and traditional Chinese medicine. *TrAC Trends in Analytical Chemistry* 2014;61:207–14. doi:10.1016/j.trac.2014.06.007
- Wang M, Chen L, Liu D, Chen H, Tang DD, Zhao YY. Metabolomics highlights pharmacological bioactivity and biochemical mechanism of traditional Chinese medicine. *Chem Biol Interact* 2017;273:133–41. doi:10.1016/j.cbi.2017.06.011
- Xiao HH, Zhang Y, Cooper R, Yao XS, Wong MS. Phytochemicals and potential health effects of *Sambucus williamsii* Hance (Jiegumu). *Chin Med* 2016;11:36. doi:10.1186/s13020-016-0106-9
- Kuang H, Tang Z, Wang X, Yang B, Wang Z, Wang Q. Chemical constituents from *Sambucus williamsii* Hance fruits and hepatoprotective effects in mouse hepatocytes. *Nat Prod Res* 2018;32(17):2008–16. doi:10.1080/14786419.2017.1361948
- Omrani VF, Koochaki A, Behzad S, Kia V, Ghasemi P, Razaviyan J, et al. Effects of *Sambucus ebulus* Extract on Cell Proliferation and Viability of Triple- Negative Breast Cancer: An In Vitro and In Vivo Study. *Anticancer Agents Med Chem* 2022;22(7):1386–96. doi:10.2174/1871520621666210412113944
- Xiao HH, Dai Y, Wong MS, Yao XS. Two new phenylpropanoids and one new sesquiterpenoid from the bioactive fraction of *Sambucus williamsii*. *J Asian Nat Prod Res* 2015;17(6):625–32. doi:10.1080/10286020.2015.1046448
- Choi H, Lee J, Chang YS, Woo ER, Lee DG. Isolation of (-)-olivil-9'-O-β-d-glucopyranoside from *Sambucus williamsii* and its antifungal effects with membrane-disruptive action. *Biochim Biophys Acta* 2013;1828(8):2002–6. doi:10.1016/j.bbame.2013.04.023
- Xiao HH, Lu L, Poon CC, Chan CO, Wang LJ, Zhu YX, et al. The lignan-rich fraction from *Sambucus Williamsii* Hance ameliorates dyslipidemia and insulin resistance and modulates gut microbiota composition in ovariectomized rats. *Biomed Pharmacother* 2021;137:111372. doi:10.1016/j.biopha.2021.111372
- Xie F, Wu CF, Zhang Y, Yao XS, Cheung PY, Chan AS, et al. Increase in bone mass and bone strength by *Sambucus williamsii* HANCE in ovariectomized rats. *Biol Pharm Bull* 2005;28(10):1879–85. doi:10.1248/bpb.28.1879
- Zhang Y, Li Q, Wan HY, Xiao HH, Lai WP, Yao XS, et al. Study of the mechanisms by which *Sambucus williamsii* HANCE extract exert protective effects against ovariectomy-induced osteoporosis in vivo. *Osteoporos Int* 2011;22(2):703–9. doi:10.1007/s00198-010-1240-3
- Xiao HH, Gao QG, Zhang Y, Wong KC, Dai Y, Yao XS, et al. Vanillic acid exerts oestrogen-like activities in osteoblast-like UMR 106 cells through MAP kinase (MEK/ERK)-mediated ER signaling pathway. *J Steroid Biochem Mol Biol* 2014;144 Pt B:382–91. doi:10.1016/j.jsbmb.2014.08.002
- Xiao HH, Dai Y, Wan HY, Wong MS, Yao XS. Bone-protective effects of bioactive fractions and ingredients in *Sambucus williamsii* HANCE. *Br J Nutr* 2011;106(12):1802–9. doi:10.1017/S0007114511002546
- Xiao HH, Dai Y, Wong MS, Yao XS. New lignans from the bioactive fraction of *Sambucus williamsii* Hance and proliferation activities on osteoblastic-like UMR106 cells. *Fitoterapia* 2014;94:29–35. doi:10.1016/j.fitote.2014.01.012
- Xiao HH, Zhu YX, Lu L, Zhou LP, Poon CC, Chan CO, et al. The Lignan-Rich Fraction from *Sambucus williamsii* Hance Exerts Bone Protective Effects via Altering Circulating Serotonin and Gut Microbiota in Rats. *Nutrients* 2022;14(22):4718.

- doi:[10.3390/nu14224718](https://doi.org/10.3390/nu14224718)
27. Xiao HH, Sham TT, Chan CO, Li MH, Chen X, Wu QC, et al. A Metabolomics Study on the Bone Protective Effects of a Lignan-Rich Fraction From *Sambucus Williamsii* Ramulus in Aged Rats. *Front Pharmacol* 2018;9:932. doi:[10.3389/fphar.2018.00932](https://doi.org/10.3389/fphar.2018.00932)
28. Xiao HH, Gao QG, Ho MX, Zhang Y, Wong KC, Dai Y, et al. An 8-O-4' norlignan exerts oestrogen-like actions in osteoblastic cells via rapid nongenomic ER signaling pathway. *J Ethnopharmacol* 2015;170:39–49. doi:[10.1016/j.jep.2015.05.012](https://doi.org/10.1016/j.jep.2015.05.012)
29. Shen YW, Cheng YA, Li Y, Li Z, Yang BY, Li X. *Sambucus williamsii* Hance maintains bone homeostasis in hyperglycemia-induced osteopenia by reversing oxidative stress via cGMP/PKG signal transduction. *Phytomedicine* 2023;110:154607. doi:[10.1016/j.phymed.2022.154607](https://doi.org/10.1016/j.phymed.2022.154607)