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Southeast Asian Medicinal Plants in Osteoporosis: A Systematic Review of Anti-Osteoclastogenesis in Preclinical Models

(Tumbuhan Ubatan Asia Tenggara untuk Osteoporosis: Ulasan Sistematik Anti-Osteoklastogenesis dalam Model Praklinikal)

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ABSTRACT

Osteoporosis is a chronic metabolic bone disorder characterised by excessive osteoclast-mediated bone resorption and compromised bone microarchitecture, especially following estrogen deficiency in postmenopausal women. Despite the availability of antiosteoporosis drugs, long-term use is limited by adverse effects, initiating the rise of research and development in plant-derived bioactive. Southeast Asia is rich in medicinal plants with reported antioxidant and estrogenic properties that may modulate bone remodelling. This systematic review aims to investigate the molecular and histomorphometric effects of Southeast Asian plant extracts on osteoblast activity and bone integrity in *in vivo* models of postmenopausal osteoporosis. This preclinical study followed PRISMA 2020 guidelines and was conducted through a systematic search of PubMed, Scopus, and ScienceDirect from 2014-2024. An extensive search was conducted across these three databases, yielding 546 articles. Sixteen articles of *in vivo* studies using an ovariectomized or postmenopausal rat models were included based on defined eligibility criteria. Risk of bias was assessed using SYRCLE's tool. A systematic review of 16 *in vivo* studies, involving 13 plant species, demonstrated consistent improvements in trabecular structure, including bone mineral density (BMD), bone volume/tissue volume (BV/TV), trabecular number (Tb.N), and trabecular thickness (Tb.Th). Plant extracts such as *Bixa orellana* L. (Annatto) and *Marantodes pumilum* var. *alata* (Kacip Fatimah) demonstrated improvement in anti-osteoclastogenesis activity by modulating signaling pathways involving RANKL, NFATc1, NF-kB, reactive oxygen species (ROS), and estrogen receptor alpha (ERα). Several compounds also enhanced osteoblast activity and bone mineral density. In conclusion, Southeast Asian plant extracts demonstrate multi-target bone-protective effects and represent promising candidates for future anti-osteoporotic therapies.

Keywords: Bone resorption; medicinal plants; osteoporosis; phytoestrogens; RANKL

ABSTRAK

Osteoporosis merupakan gangguan metabolik tulang kronik yang dicirikan oleh aktiviti osteoklas berlebihan, mengakibatkan peningkatan penyerapan tulang serta kemerosotan mikroarkitektur tulang, terutamanya disebabkan kekurangan estrogen dalam kalangan wanita pascamenopaus. Walaupun ubat antiosteoporosis tersedia, penggunaannya dalam jangka panjang adalah terhad akibat kesan sampingan, sekali gus mendorong penyelidikan dan pembangunan bioaktif berasaskan tumbuhan. Asia Tenggara kaya dengan tumbuhan ubatan yang dilaporkan mempunyai sifat antioksidan dan estrogen yang berpotensi memodulasi pembentukan semula tulang. Ulasan sistematik ini bertujuan untuk menilai kesan molekul dan histomorfometrik ekstrak tumbuhan Asia Tenggara terhadap aktiviti osteoblas dan integriti tulang dalam model *in vivo* osteoporosis pascamenopaus. Kajian praklinikal ini mengikuti garis panduan PRISMA 2020 dan dijalankan melalui carian sistematik dalam pangkalan data PubMed, Scopus dan ScienceDirect bagi tempoh 2014-2024. Carian menyeluruh daripada tiga pangkalan data menghasilkan sejumlah 546 artikel. Sebanyak 16 artikel kajian *in vivo* menggunakan model tikus ovariektomi atau pascamenopaus dipilih berdasarkan kriteria kelayakan yang ditetapkan. Risiko berat sebelah dinilai menggunakan alat SYRCLE. Ulasan sistematik terhadap 16 kajian *in vivo* melibatkan 13 spesies tumbuhan menunjukkan peningkatan yang konsisten dalam struktur trabekular, termasuk ketumpatan mineral tulang (BMD), isi padu tulang/isi padu tisu (BV/TV), bilangan trabekular (Tb.N) dan ketebalan trabekular (Tb.Th). Ekstrak tumbuhan seperti *Bixa orellana* L. (Annatto) dan *Marantodes pumilum* var. *alata* (Kacip Fatimah) menunjukkan aktiviti anti-osteoklastogenesis melalui pengawalaturan tapak jalan isyarat yang melibatkan RANKL, NFATc1, NF-κB, spesies oksigen reaktif (ROS) dan reseptor estrogen alfa (ERα). Beberapa sebatian juga didapati meningkatkan aktiviti osteoblas dan ketumpatan mineral tulang.

Kesimpulannya, ekstrak tumbuhan Asia Tenggara menunjukkan kesan pelindung tulang pelbagai sasaran dan berpotensi untuk dijadikan calon terapi antiosteoporosis pada masa hadapan.

Kata kunci: Fitoestrogen; osteoporosis; penyerapan tulang; RANKL; tumbuhan ubatan

INTRODUCTION

Osteoporosis is a chronic skeletal disorder characterised by decreased bone mass and deterioration of the bone microarchitecture, which increases the risk of skeletal fractures (Salari et al. 2021). It may arise from an imbalance in the bone remodelling process that is triggered by an alteration in the biological equilibrium between osteoclasts and osteoblasts, where the former resorbs the bone and the latter forms new bone (Hadjidakis & Androulakis 2006; Rowe, Koller & Sharma 2023). In post-menopausal women, estrogen deficiency leads to accelerated bone turnover by upregulating RANKL and downregulating OPG, leading to increased osteoclastogenesis and excessive bone resorption (Cauley et al. 2012; Cheng, Chen & Chen 2022).

The modern antiresorptive treatments, such as bisphosphonates, denosumab, and selective estrogen receptor modulators (SERMs) have been shown to decrease the chances of fractures. Unfortunately, these medications are associated with long-term complications like osteonecrosis of the jaw, atypical femoral fractures, and renal impairment (Gupta & Gupta 2023; Kendler et al. 2022; McClung et al. 2012). This has sparked interest in alternative, plant-based treatments that have osteoprotective benefits (De Martinis, Sirufo & Ginaldi 2020; Karimi et al. 2025; Martiniakova, Babikova & Omelka 2020).

Southeast Asia is home to several species of medicinal plants whose traditional uses include treating bone disorders. Such plants contain bioactive compounds, including tocotrienols, flavonoids, and polyphenols, which are known to improve bone health due to their antioxidant properties, estrogen receptor agonism, and inhibition of the RANKL signalling pathway (Korani et al. 2024; Sanusi et al. 2017). Tocotrienols from *Bixa orelllana* L. and polyphenols from *Marantodes pumilum* (Blume) Kuntze var. *alata* have potent anti-osteoclastogenic activity by altering the RANKL/OPG ratio and lowering oxidative stress (Mohamad et al. 2021b).

Plant-based treatments for osteoporosis have been studied in preclinical settings; however, the literature has little to no focus on this topic due to reviewers' tendency to generalise findings across species or centre on osteoblast function. So far, there is no systematic review that specifically focuses on the *in vivo* molecular effects of Southeast Asian medicinal plant extracts on osteoclast regulation and bone microarchitecture in postmenopausal osteoporosis models. This regional and mechanistic gap limits the translational application of locally relevant phytomedicine into anti-resorptive strategies. To address this, the present review critically analysed the *in vivo* effects of Southeast Asian plant extracts on osteoclast-related molecular pathways and bone structure integrity in established animal models. By focusing on the effective and safe regional plant extracts with plausible mechanisms of action, this review aims to support the rational development of phytotherapeutic interventions for osteoporosis management.

MATERIALS AND METHODS

This systematic review was conducted in according with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines (Page et al. 2021). The review protocol followed rigorous inclusion and exclusion criteria and included a risk bias assessment based on SYCLE's RoB tool for animal studies (Hooijmans et al. 2014).

SEARCH STRATEGY

A comprehensive literature search was conducted across PubMed, Scopus, and ScienceDirect databases to identify relevant *in vivo* studies published between 2014 and 2024. The search terms that were applied are an integration of ((‘Plant Extracts’[MeSH] OR ‘Phytochemicals’[MeSH] OR ‘Herbal Medicine’[MeSH] OR ‘Botanical Extracts’) and (‘Osteoporosis’[MeSH] OR ‘Bone Density’ OR ‘Bone Loss’ OR ‘Bone Resorption’)) AND (‘Animal Study’ OR ‘*In vivo*’) in PubMed.

For Scopus, the search terms were (‘plant extract*’ OR ‘phytochemical* OR ‘herbal medicine’ OR ‘botanical extract*’) AND (‘osteoporosis’ OR ‘bone density’ OR ‘bone loss’ OR ‘bone resorption’).

For ScienceDirect was (‘plant extract’ OR ‘herbal medicine’) AND (‘osteoporosis’ OR ‘bone loss’) AND (clinical trial OR animal study OR safety OR ‘adverse effects’). These keywords were combined using Boolean Operators ‘OR’ for synonyms of the same category and ‘AND’ operator to combine two or more categories.

ELIGIBILITY CRITERIA

The systematic review was conducted between January and December 2024 by Y.S., hence the review included full-text articles published in English between 2014 and 2024. Eligible studies were preclinical *in vivo* investigations on plant extracts or natural compounds derived from Southeast Asian countries, using female, postmenopausal, or ovariectomized rats. Studies were required to assess bone-related parameters such as trabecular structure, bone mineral density, or biochemical markers.

Exclusion criteria comprised duplicate publications, reviews, abstracts, conference proceedings, and non-research materials. *In vitro* studies, male animal models, non-osteoporotic models, and studies involving non-Southeast Asian plant sources were excluded.

STUDY SELECTION AND DATA EXTRACTION

A total of 546 articles were initially identified through database searches. Two independent reviewers (Y.S. and I.Z.Z.A.) screened the titles and abstracts after removing duplicate articles, applying the predefined inclusion and exclusion criteria, which produced 19 potentially relevant articles. Any reviewer disagreement was resolved through consensus in collaboration with a third reviewer (S.H.Z.A.). Following full-text assessment, three articles were excluded due to the unavailability of full-text data, resulting in 16 articles that were eligible for inclusion in this review. Key information extracted from the selected studies included the plant species and extract type, country of origin, identified bioactive compounds, animal model characteristics, bone-related parameters and histological findings, as well as reported mechanisms of action, especially those related to osteoclast modulation.

RISK OF BIAS ASSESSMENT

The risk of bias was assessed using the Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) tool (Hooijmans et al. 2014), which evaluates selection, performance, detection, attrition, reporting, and other potential sources of bias in preclinical animal studies. Two reviewers (Y.S. and I.Z.Z.A.) independently assessed all studies, resolving discrepancies by consensus. This approach ensures inclusion of high-quality, translationally relevant preclinical evidence aligned with PRISMA and SYRCLE standards. Bias levels were categorised as low, high, or unclear.

RESULTS AND DISCUSSION

An exhaustive search on PubMed, Scopus, and ScienceDirect resulted in 546 articles. Following thorough screening according to PRISMA's rules, 16 *in vivo* studies that utilized ovariectomized or postmenopausal rat models were chosen for further evaluation (Figure 1). These studies assessed the molecular and structural impacts of plant extracts from Southeast Asian on osteoclasts and the microarchitecture of bones.

PLANT EXTRACT DISTRIBUTION AND MOLECULAR RELEVANCE

Table 1 details the 13 different plant species (two plants involved more than one study), their common names, and regional presence. Although not all plants were endemic, each had widespread cultivation or traditional use in Southeast Asia, hence making them relevant for further development in regional therapeutic contexts. Notably, *Marantodes pumilum* (Blume) Kuntze var. *alata* (Kacip Fatimah) and *Bixa orellana* L. (Annatto) were native to Malaysia and showed repeated molecular efficacy in multiple studies (Chin et al. 2017; Gaize et al. 2019, 2018; Mohamad, Ima-Nirwana & Chin 2021a, 2021b).

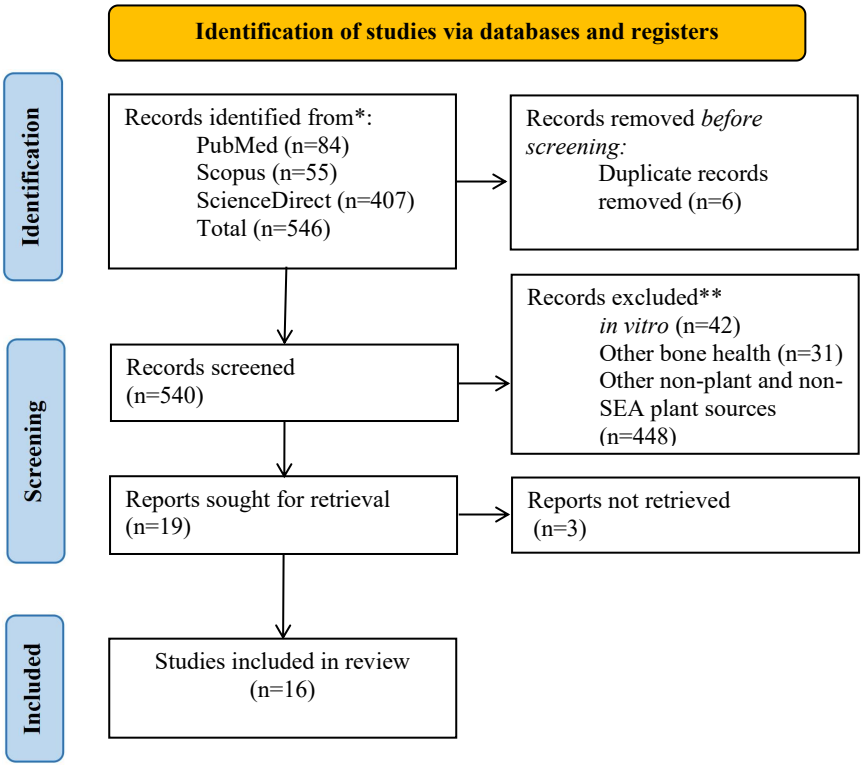

FIGURE 1. PRISMA flow diagram showing study selection process for Southeast Asian medicinal plants in Osteoporosis Research

TABLE 1. Plant and country of origin, cultivation or distribution in Southeast Asia

No.	Plant	Common name	Country (Reference)
1.	*Psoralea corylifolia* L.	Babchi or Malay tea	Malaysia, Myanmar, Indonesia, Vietnam (Xu et al. 2023)
2.	*Andrographis paniculata* (Burm.f.) Wall. ex Nees	Hempedu Bumi	Malaysia, Indonesia, Laos, Myanmar, Thailand, Vietnam (Chang et al. 2019)
3.	*Cicer arietinum* L.	Chickpea	Myanmar (Huang et al. 2024)
4.	*Dioscorea alata* L.	Yam	Malaysia, Indonesia, Myanmar, Thailand, Philippines (Chatan et al. 2023)
5.	*Boehmeria nivea* (L.) Gaudich	Ramie leaves	Malaysia (Malay Peninsula), Philippines (Lee et al. 2023)
6.	*Eleutherine bulbosa* (Mill.) Urb.	Dayak onion	Malaysia, Indonesia, Brunei (Luthfiana et al. 2023)
7.	*Bixa orellana* L.	Annatto	Malaysia, Indonesia (Chin et al. 2017; Mohamad, Ima-Nirwana & Chin 2021a; Mohamad, Ima-Nirwana & Chin 2021b)
8.	*Marantodes pumilum* (Blume) Kuntze var. alata	Kacip Fatimah	Malaysia (Giaze et al. 2019, 2018)
9.	*Morinda citrifolia* L.	Mengkudu	Malaysia (Wattanathorn et al. 2018)
10.	*Cinnamomum burmannii* (Nees & T.Nees) Blume	Cinnamon	Indonesia, Vietnam, Myanmar (Kania et al. 2018)
11.	*Solanum nigrum* L.	European black nightshade	Malaysia (Kim et al. 2021)
12.	*Centella asiatica* (L.) Urb.	Asiatic pennywort	Malaysia, Indonesia (Wang et al. 2018)
13.	*Bombax ceiba* L.	Red silk-cotton tree	Malaysia (Chauhan et al. 2018)

PLANT-SPECIFIC EFFECTS ON BONE MICROARCHITECTURE

Table 2 presents an integrative comparison of Southeast Asia medicinal plants with demonstrated anti-osteoporotic potential. This correlates each plant's traditional ethnomedicinal use, extent of documentation, and known bioactive compounds with validated *in vivo* bone protective findings from this review. This integrative approach enables the evaluation of which the literature more strongly supports traditional uses and highlights the molecular mechanisms that bridge traditional knowledge with contemporary preclinical findings.

Histomorphometric analysis showed that the majority of extracts demonstrated improvements in trabecular architecture, particularly in Bone Volume per Tissue Volume (BV/TV), Number (Tb.N), and Thickness (Tb.Th). The osteoclast-inhibiting effect of each extract was evaluated using either histomorphometric markers or biochemical indicators, such as CTX and Alkaline phosphatase (ALP). ALP also serves as a biomarker of osteoblast differentiation (Intan Zarina et al. 2022, 2010; Rohaya et al. 2017; Shahrul Hisham et al. 2024) and has been utilised to evaluate dental canine movement and root resorption during orthodontic treatment (Rohaya et al. 2015).

The decrease in osteoblast numbers and increase in trabecular density have been associated with the use of *Psoralea corylifolia* L. (Xu et al. 2023). *Andrographis paniculata* (Burm.f.) Wall. ex Nees has been documented to improve bone density and trabecular structure (Chang et al. 2019). *Cicer arietinum* L. (chickpea) was found to enhance trabecular microstructure and alter estrogen receptor alpha (ERα), suggesting phytoestrogenic activity (Table 2) (Huang et al. 2024).

Dioscorea alata L. demonstrated trabecular bones thickening, thereby improving bone density (Chatan et al. 2023). Additionally, *Boehmeria nivea* (L.) Gaudich (Ramie leaf) showed a reduction in cathepsin K expression, a protease critical to osteoclast function, while also restoring trabecular bone (Lee et al. 2023). *Eleutherine bulbosa* (Mill.) Urb. increased bone density and osteoblast levels, indicating dual modulation of both osteoclasts and osteoblasts (Table 2) (Luthfiana et al. 2023).

Morinda citrifolia L. enhanced trabecular bone volume and mineral density while reducing osteoclast density and increasing serum calcium levels (Wattanathorn et al. 2018). *Cinnamomum burmannii* (Nees & T.Nees) Blume, on the other hand, increased osteocalcin levels and decreased

bone oxidative stress (Kania et al. 2018). *Solanum nigrum* L. exhibited improvement in bone mineral density and trabecular number while reducing osteoclast density and increasing serum calcium levels (Table 2) (Kim et al. 2021).

Bombax ceiba L. is credited with the increase of bone mineral density, trabecular number and trabecular thickness (Chauhan et al. 2018), while *Centella asiatica* (L.) Urb. has been shown to increase osteocalcin levels and enhance bone volume/tissue volume (BV/TV) ratio and trabecular number (Table 2) (Wang et al. 2018).

Overall, the integrative evaluation of the reviewed studies indicates a strong correlation between traditional ethnomedicinal uses and experimental evidence of anti-osteoporotic activity. *Marantodes pumilum* (Blume) Kuntze var. *alata* (Kacip Fatimah) and *Bixa orellana* L. show the most consistent and well-supported findings, where improvements in bone microarchitecture and suppression of osteoclastogenesis substantiate their traditional use for women's health and bone strength. The involvement of bioactive compounds such as δ- and γ-tocotrienols, gallic acid, and ellagic acid, which modulate RANKL/OPG, BV/TV ratios, and trabecular mineralisation, validates their long-practised ethnomedicinal claims and underscores their potential as promising natural agents for osteoporosis management.

POTENT AND CONSISTENT COMPOUND: *Bixa orellana* L. AND *Marantodes pumilum* (Blume) Kuntze var. *alata*

Based on the compounds' studies, the tocotrienols from *Bixa Orellana* and phenolic acid (gallic, and ellagic acids) from *Marantodes pumilum* (Blume) Kuntze var. *alata* stood out as the most potent and consistent structural bone-enhancing compounds. *Bixa orellana* L. also demonstrated increases in trabecular number and volume with a profound decrease in the RANKL/OPG ratio, which is a key of osteoclastogenesis suppression (Chin et al. 2017; Mohamad, Ima-Nirwana & Chin 2021a, 2021b). *Marantodes pumilum* (Blume) Kuntze var. *alata* demonstrated antioxidant-mediated protection against oxidative stress-induced bone loss (Giaze et al. 2019, 2018), the main contributor to postmenopausal osteoporosis (Table 2). The polyphenols not only improved bone structural parameters but also significantly modulated systemic markers.

These findings demonstrate that Southeast Asian plant extracts consistently improve main structural bone parameters, with effective improvement observed in the trabecular architecture, bone mineral density, and cellular bone markers. These articles suggest therapeutic potential for addressing osteoporotic bone loss.

MECHANISMS OF ACTION

The Southeast Asian plant extracts demonstrated diverse molecular mechanisms targeting osteoclast activity and bone remodeling pathways. The primary mechanism involves the inhibition of RANKL-mediated osteoclastogenesis, with multiple studies reporting significant downregulation of NFATc1, a master transcription factor that regulates osteoclast differentiation and function (Chang et al. 2019; Huang et al. 2024; Xu et al. 2023). *Psoralea corylifolia*-derived Coryfol A specifically attenuated RANKL-induced osteoclastogenesis through ROS reduction, ERK inhibition, and NFATc1 activation suppression in ovariectomized rats (Xu et al. 2023). Similarly, *Andrographis paniculata* (Burm.f.) Wall. ex Nees, containing andrographolide, stimulated osteoblastogenesis while simultaneously inhibiting osteoclast formation via suppression of nuclear factor kappa-B (NF-kB) signalling, thereby demonstrating dual regulatory effects on bone remodelling (Chang et al. 2019) (Figure 2).

Targeting the activation of osteoclasts by reactive oxygen species (ROS) has received much attention, considering how oxidative stress modulation serves as a pivotal pathway. Extracts from the leaves of *Boehmeria nivea* (L.) Gaudich (Ramie) mitigated bone depletion in ovariectomized rats by actively participating in ROS reduction and its downstream signaling pathways (Lee et al. 2023) (Figure 2). This antioxidant-based approach is a novel therapeutic strategy distinct from conventional anti-resorptive methods.

The mechanisms of phytoestrogens were illustrated with several plants from Southeast Asia (Figure 2). *Cicer arietinum* L. (Chickpea) isoflavones exhibit advanced dual regulation of bone remodelling via ERα, which stimulates osteoblast activity and inhibits osteoclast differentiation in osteoporotic conditions following ovariectomy (Huang et al. 2024) (Figure 2). *Morinda citrifolia* L. also showed estrogenic effects by protecting against menopause-induced cerebral ischemia and osteoporosis (Wattanathorn et al. 2018). *Dioscorea alata* L. ethanol extract addressed complicated interactions between metabolic disorders with bone loss by improving insulin resistance coupled with estrogen deficiency in type 2 diabetic ovariectomized rats (Chatan et al. 2023) (Figure 2).

Novel mechanistic pathways were identified in several species. *Centella asiatica* (L.) Urb. derived madecassoside inhibited estrogen deficiency-induced osteoporosis through specific suppression of RANKL-induced osteoclastogenesis, demonstrating selective targeting of pathological bone resorption (Wang et al. 2018). *Cinnamomum burmannii* (Nees & T.Nees) Blume extract exhibited unique systemic bone-regenerative effects by modulating osteocalcin expression and favourably shifting the RANKL/OPG ratio, with histomorphometric evidence showing tibial granule formation in ovariectomized rats (Kania et al. 2018) (Figure 2).

Additional mechanisms also include *Solanum nigrum* L., which directly inhibits osteoclast differentiation (Kim et al. 2021), and glucocorticoid-induced rats, showing the osteoporosis-protective effects of *Eleutherine*

TABLE 2. Integrated analysis linking traditional uses, bioactive compounds, and preclinical findings of Southeast Asian medicinal plants with documented anti-osteoporotic effects

Plant (scientific name, author abbreviation)	Traditional benefit (B) and Evidence (E)	Principal bioactive compound(s)	*In vivo* effects on bone	Integrative evaluation	References
Psoralea corylifolia L.	**B**: Used in Ayurveda and Malay medicine for bone healing and female vitality **E**: Widely documented in South and Southeast Asia	Corylifol A	↓ osteoclast number; ↑ BV/TV and Tb.N; ROS ↓; NFATc1 ↓	Anti-resorptive and antioxidant actions validate the folkloric use of bone-strengthening agents	Xu et al. (2023)
Andrographis paniculata (Burm.f.) Wall. ex Nees	**B**: Anti-inflammatory tonic for postpartum recovery **E**: Broad regional use in Malay-Thai- Indian systems	Andrographolide	↑ BMD; improved trabecular structure; NF-κB and RANKL ↓	Robust evidence linking anti-inflammatory activity with osteoprotective effect	Chang et al. (2019)
Cicer arietinum L.	**B**: Enhances female hormonal balance and bone health **E**: Dietary and ethnomedicinally common	Biochanin A, Formononetin, Sissotrin	Improved trabecular microstructure; ERα activation	Phytoestrogenic mechanism substantiates the traditional menopausal-bone claim	Huang et al. (2024)
Dioscorea alata L.	**B**: Tonic for postmenopausal and metabolic wellbeing **E**: Widely consumed yam species	Diosgenin	↑ Tb.Th and BMD; modulated estrogen and lipid metabolism	Well-supported link between estrogenic effect and traditional vitality claims	Chatan et al. (2023)
Boehmeria nivea (L.) Gaudich	**B**: Remedy for fractures and inflammation **E**: Regionally recorded folk use	Canthaxanthin	↓ cathepsin K; oxidative stress ↓; trabecular bone ↑	Mechanistic anti-resorptive effects confirm ethnomedicinal claim	Lee et al. (2023)
Eleutherine bulbosa (Mill.) Urb.	**B**: Postpartum restorative and wound-healing herb in Borneo **E**: Localised but consistent ethnomedical record	Phenanthrene, Cuspidatumin A, Dendromoniliside E, Liquiritigenin, Natsudaidain	Prevented glucocorticoid-induced bone loss; ↑ osteoblast activity	Provides modern validation of traditional recovery use	Luthfiana et al. (2023)

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Bixa orellana L.	**B**: Tonic and antioxidant plant **E**: Common and well-documented in tropical folk medicine	δ- and γ-tocotrienols	↑ trabecular mineralisation; ↓ RANKL/OPG ratio	Strong evidence supports antioxidant and bone-protective traditional use	Chin et al. (2017); Mohamad, Ima-Nirwana & Chin (2021a, 2021b)
Marantodes pumilum (Blume) Kuntze var. alata	**B**: 'Kacip Fatimah'; postpartum and women's vitality herb **E**: Highly established in Malay traditional medicine	Gallic acid, Ellagic acid	↑ BMD and BV/TV; ↓ oxidative stress	Well-supported traditional claims; confirmed by consistent *in vivo* data	Giaze et al. (2018); Giaze et al. (2019)
Morinda citrifolia L.	**B**: Used for vitality and ageing weakness **E**: Pan-Pacific traditional tonic	Rutin, Gallic acid	↑ BV/TV and Ca^{2+}; ↓ osteoclasts	Aligned with traditional rejuvenating and bone integrity effects	Wattanathorn et al. (2018)
Cinnamomum burmannii (Nees & T.Nees) Blume	**B**: Improves blood circulation and joint health **E**: Widely practised Indonesian folk use	Eugenol, Coumarin, Trans-cinnamic acid	↑ osteocalcin; improved RANKL/OPG balance	Molecular findings validate musculoskeletal vitality claim	Kania et al. (2018)
Solanum nigrum L.	**B**: Anti-inflammatory and postpartum remedy **E**: Common regional household medicine	Eugenol, Coumarin, Trans-cinnamic acid	↑ BMD; ↓ osteoclasts; ↑ Ca^{2+}	Supported by clear in vivo anti-resorptive and calcium-preserving actions	Kim et al. (2021)
Centella asiatica (L.) Urb.	**B**: Promotes tissue repair and wound healing **E**: Long-established in Malay and Ayurvedic systems	Madecassoside	Inhibited RANKL-induced osteoclastogenesis; ↑ BV/TV	Mechanistic support extends the traditional tissue-healing claim to bone health	Wang et al. (2018)
Bombax ceiba L.	**B**: Used for bone fracture and reproductive disorders **E**: Common in Indian-Malay traditional practice	Lupeol, β-sitosterol, Gallic acid	↑ Tb.Th, Tb.N, BMD in OVX models	Provides strong mechanistic validation of the fracture-healing reputation	Chauhan et al. (2018)

↓; Increased expression or activity, ↓; decreased expression or activity, BMD; Bone Mineral Density, BV/TV; bone volume/tissue volume, Tb.N; trabecular number, Tb.Th; trabecular thickness, ROS; Reactive oxygen species, NFATc1; Nuclear factor of activated T-cells cytoplasmic 1, NF-κB; Nuclear factor kappa-light-chain-enhancer of activated B cells, RANKL; Receptor activator of nuclear factor kappa-B ligand, RANKL/OPG ratio; RANKL / osteoprotegerin ratio, OVX; Ovariectomized (rat) model

bulbosa (Mill.) Urb. (Luthfiana et al. 2023). *Bombax ceiba* L. exhibited dual activity through quantified compounds, such as lupeol, gallic acid, and β-sitosterol, stimulating *in vitr*o osteoblast proliferation and demonstrating *in vivo* anti-osteoporotic effects (Chauhan et al. 2018) (Figure 2).

Time series analyses have shown that these various mechanisms are maintained throughout the 4-12-week treatment period, with the majority of studies showing marked improvement in bone parameters within 6-8 weeks of intervention. The dose-response relationship exhibits significant variability across species (10-500 mg/kg body weight), highlighting the chemical diversity and varying potencies of medicinal plants from Southeast Asia. It is noteworthy that numerous extracts displaying a multitarget approach suggest advantages over interventions that operate through a single pathway when dealing with multifaceted osteoporotic conditions.

As for the potent and consistent tocotrienol-rich *Bixa orellana* L. extract demonstrated advanced therapeutic potential through multiple mechanisms, i.e., suppression of skeletal sclerostin levels, modulation of RANKL/OPG ratios, and enhancement of bone morphogenetic protein-2 (BMP-2) expression (Chin et al. 2017; Mohamad, Ima-Nirwana & Chin 2021a, 2021b) (Figure 2). The self-emulsifying drug delivery systems significantly improved bioavailability and therapeutic efficacy, indicating the significance of formulation strategies for plant-based osteoporosis interventions. On the other hand, *Marantodes pumilum* (Blume) Kuntze var. *alata* exerts anti-osteoporotic effect primarily through its phenolic compounds, especially Gallic acid and Ellagic acid. Gallic acid was more abundant in the leaf extract and acts as a phytoestrogen by binding to estrogen receptors in promoting osteoblast activity and suppressing osteoclast-mediated bone resorption. Gallic acid also enhances antioxidant defences, hence protecting bone microarchitecture from oxidative damage. Ellagic acid which is more concentrated in the root also contribute to anti-osteoporotic effect but with lower potency. These mechanisms overall support *Marantodes pumilum* (Blume) Kuntze var. *alata* traditional use in postmenopausal bone health (Giaze et al. 2019, 2018).

RISK OF BIAS ASSESSMENT

Utilising the SYCLE's tool (Hooijmans et al. 2014), most studies exhibited a low risk of bias, especially in sequence generation and outcome reporting, with only three studies rated as having moderate risk (Table 3). In contrast, the risks of performance and detection bias were often unclear due

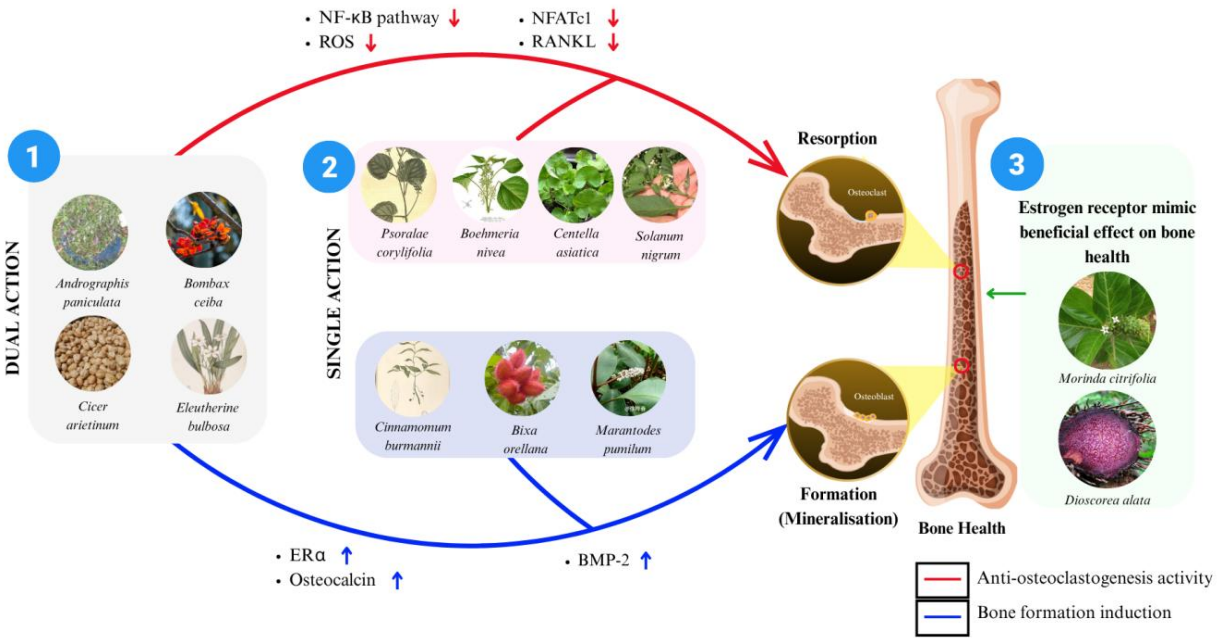

FIGURE 2. Osteoprotective and anti-osteoclastogenesis effect of plant extracts for bone health. The mechanism of action of Southeast Asian plants in maintaining bone health generally consisted of three primary mechanisms for bone health maintenance, i.e. 1) Direct dual actions of bone promotion and anti-osteoclastogenesis effects or protective effects in glucocorticoid-induced osteoporosis models. 2) Single action either through bone formation induction or anti-osteoclastogenesis activity, and 3) Estrogen receptor induction mimics the beneficial effect on bone health. Estrogen receptor mediated induction exhibited dual actions of enhancing bone formation and also anti-osteoclastogenesis that inhibit osteoclast formation

TABLE 3. SYRCLE's Risk of Bias Assessment for Included Studies Using SYRCLE's Tool

Reference	1	2	3	4	5	6	7	8	9	10	Summary
Xu et al. (2023)	L	H	L	L	U	U	U	L	L	L	Low risk
Chang et al. (2019)	L	H	H	U	U	U	U	L	L	L	Moderate risk
Huang et al. (2024)	L	L	L	L	U	U	U	L	L	L	Low risk
Chatan et al. (2023)	L	L	L	L	U	U	U	L	L	L	Low risk
Lee et al. (2023)	L	H	L	U	U	U	U	L	L	U	Low risk
Luthfiana et al. (2023)	L	L	H	U	U	U	U	L	L	H	Moderate risk
Mohamad, Ima-Nirwana & Chin (2021a)	L	L	L	L	U	U	U	L	L	U	Low risk
Mohamad, Ima-Nirwana & Chin (2021b)	L	L	L	L	U	U	U	L	L	L	Low risk
Chin et al. (2017)	L	L	L	L	U	U	U	L	L	U	Low risk
Giaze et al. (2019)	L	L	H	U	U	U	U	L	L	U	Low risk
Giaze et al. (2018)	L	L	L	L	U	U	U	L	L	L	Low risk
Wattanathorn et al. (2018)	L	L	L	L	L	U	U	L	L	U	Low risk
Kania et al. (2018)	L	L	L	L	U	U	U	L	L	L	Low risk
Kim et al. (2021)	L	L	L	L	U	U	U	L	L	U	Low risk
Wang et al. (2018)	L	H	H	L	U	U	U	L	L	U	Moderate risk
Chauhan et al. (2018)	L	L	L	L	U	U	U	L	L	L	Low risk

H; High Risk of Bias, L; Low Risk of Bias, U; Unclear, 1; Sequence Generation, 2; Baseline Characteristics, 3; Allocation Concealment, 4; Random Housing, 5; Blinding (Performance Bias), 6; Random Outcome Assessment, 7; Blinding (Detection Bias), 8; Incomplete Outcome Data, 9; Selective Outcome Reporting, 10; Other Sources of Bias

to the lack of reported randomisation or blinding protocols. Overall, the internal validity of the included studies was considered acceptable for a preclinical systematic review.

LIMITATION

Although the review shows a potential molecular effect, this systematic review has several limitations when interpreting the findings. Firstly, although all included studies follow the predefined inclusion criteria, the overall number of high-quality *in vivo* studies evaluating Southeast Asian plant extracts for osteoclast modulation remains limited. The small sample size of studies reduces the generalization and robustness of the conclusion. Secondly, considerable heterogeneity was observed across studies in terms of plant species used, extraction methods, dosing, duration of treatment, and outcome measures. These methodological variations limit direct comparison and could contribute to inconsistencies in the reported effects. In addition, most studies did not report pharmacokinetic properties, bioavailability, or potential toxicity, which limits the translational relevance and safety for clinical use. Most of the studies included were based on the ovariectomized rat models, which are accepted as a postmenopausal osteoporosis model but do not fully replicate the pathophysiology of osteoporosis in humans. Despite these limitations, this review provides an important insight into the molecular effects of Southeast Asian plant extracts on osteoclast activity. Future studies should focus on addressing these gaps through standardized experimental protocols, comprehensive toxicological evaluation, and clinical validation studies.

CONCLUSION

This systematic review highlights the potential of Southeast Asian medicinal plants supported by both traditional use and preclinical evidence as promising anti-osteoporotic agents through multi-target action on the bone remodelling pathway. Integrated analysis of recent findings confirms that *Bixa orellana* L. (Annatto) and *Marantodes pumilum* (Blume) Kuntze var. *alata* (Kacip Fatimah) are the most consistently validated species, showing improvement in bone microarchitecture by suppressing RANKL-mediated osteoclastogenesis through antioxidant and estrogen-like mechanisms. Other plants, such as *Psoralea corylifolia* L., *Dioscorea alata* L. and *Centella asiatica* (L.) Urb., exhibit complementary osteoprotective actions that further support traditional claims of bone-strengthening effects. Collectively, phytochemicals such as Tocotrienols, Diosgenin, Andrographolide, and Corylifol A can modulate oxidative stress and key signalling pathways (RANKL/OPG/NFATc1), supporting their role in inhibiting bone resorption and promoting formation. Overall, these findings reinforce the long-practised ethnomedicinal traditions and provide a fundamental basis for further pharmacological standardisation, mechanistic exploration, and clinical validation of Southeast Asian phytomedicines as complementary strategies for osteoporosis management.

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