REVIEW ARTICLE

Osteoporosis: Its Mainstream Treatments and Potential Prevention with Phytochemicals: A Review

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ABSTRACT

Osteoporosis is known as a common skeletal condition marked by reduced bone strength, which results in a higher likelihood of fractures, particularly among the elderly. This disease affects millions globally, posing significant burden on patients and healthcare systems. Current pharmacological treatment, including bisphosphonates, denosumab, and teriparatide, are effective but associated with adverse effects over long-term use. Non-pharmacological approaches, such as calcium supplementation and vitamin D, are also common without risks but not when taken in excess. As interest grows in natural alternatives approach, this review explores the potential of phytochemicals which exhibit unique bioactive properties such as *Eurycoma longifolia, Labisia pumila, Piper sarmentosum, Herba epimedii, Glycine max,* and *Psoralea corylifolia* in preventing and treating osteoporosis. The review critically compares the advantages and limitations of phytochemical approaches against conventional treatments, advocating further research into their safety and efficacy as complementary options for managing osteoporosis.
Malaysian Journal of Medicine and Health Sciences (2025) 21(5): 316-327. doi:10.47836/mjmhs.21.5.35

Keywords: Treatment, Prevention, Phytochemicals, Osteoporosis, Mainstream treatments

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INTRODUCTION

Osteoporosis is known as the world's most prevalent bone disease, contributing to a growing social and economic strain. This silent disease, often undetected until fractures occur, affects millions globally, particularly the elderly. This disease's symptoms comprised of low bone density (BMD), bone tissue deterioration, as well as an elevated risk of fractures caused by decreased bone strength (1). Clinically, BMD is assessed using dual-energy X-ray absorptiometry (DXA), known as a non-invasive method. With regard to diagnosing osteoporosis, the World Health Organization (WHO) recommends that BMD, as well as fractures serve as the primary indicators. A low BMD indicates an increased fracture risk, as shown by epidemiological studies. According to WHO (Table I), an individual with low BMD or the most negative T-score value is classified as having osteoporosis (2). Current mainstream treatments for osteoporosis include pharmacological options such as bisphosphonates, denosumab, and teriparatide, as well as non-pharmacological approaches like lifestyle modifications, vitamin D and calcium supplementation, as well as physical activity (3,4). However, these treatments often come with limitations and side effects, prompting the need for alternative solutions. In recent years, interest was observed to increase in utilising phytochemicals from natural herbs as potential agents for the prevention as well as treatment with regard to osteoporosis. These herbal therapies, known for their mild and gradual effects, focus on prevention and maintenance rather than aggressive treatment, making them an attractive alternative. Hence, this review paper provides an overview of osteoporosis, focusing on both conventional treatments and the potential role of natural herbs in treatment and prevention of osteoporosis commonly found in Asia.

Table I: WHO criteria for clinical diagnosis for osteoporosis.

BMD T-score	Diagnosis
T-score ≥ -1	Normal
-1 > T-score > 2.5	Low bone mass
T-score ≤ -2.5	Osteoporosis
T-score ≤ -2.5 with existing fracture	Severe osteoporosis

OSTEOPOROSIS

Osteoporosis is particularly in Asia, with projected 3.5-fold increase in hip fracture by the year 2050 (5). Even though Asia faces a higher risk of osteoporosis, diagnosis and treatment options remain limited, particularly

in rural areas where individuals are often treated conservatively at home instead of receiving surgery in hospitals. In Malaysia, the Chinese population has the highest rate of osteoporosis (62%), followed by Malays, Indians, and others (6). Consequently, the financial burden of osteoporosis weighs heavily on patients. The economic burden became significant, with healthcare costs reaching over MYR540 million annually in Malaysia (5,7).

While the mortality rate with regard to hip fractures in East Asia is lower compared to the United States (US) as well as the United Kingdom (UK), the limited awareness concerning osteoporosis in Asia contributes to a notable increase in mortality (8). Osteoporosis is common among Caucasians, women, and the elderly but it is becoming more prevalent in both genders as the population ages (1). Moreover, women experience fractures more frequently than men due to their tendency to lose bone at a faster rate and at a younger age. Consequently, the fracture risk for women is twice than that of men of same age. In 2005, there existed 1.45 million fractures among US women over 50, in comparison to 594,000 in men (9). Similarly, osteoporosis is a condition that impacts the elderly. Note that ageing, along with the genetic, hormonal and lifestyle factors, contributes to increased bone loss and fracture risk (10). Bone tissue undergoes continuous renewal to replace both new and damaged bones, necessitating the maintenance of BMD and the integrity of its crystals and structure. Individuals typically reach peak BMD in their late 20s to mid-30s, after which, starting around age 35, bone deterioration begins. As people age, their bones are resorbed more rapidly than they are formed, leading to osteoporosis.

Osteoporosis may be categorised into primary, associated with age and gender, and secondary, affected by lifestyle and medical conditions. In primary osteoporosis, age-related bone degradation occurs, with oestrogen reduction in women and testosterone inhibition in men leading to bone loss (3,11). Secondary osteoporosis in men is often related to lifestyle factors, while in women, it can be caused by conditions like vitamin D deficiency, endocrine disorders, and calcium metabolism issues (11,12).

PHYTOCHEMICALS IN PREVENTION AND TREATMENT OF OSTEOPOROSIS

Traditional treatments for diseases often involved the use of natural plants by older generations. Recently, researchers have begun to investigate these natural plants, especially for their potential in preventing osteoporosis (13). These herbs were highlighted in this review for osteoporosis treatment due to their distinct bioactive compound that specifically target bone health, hormonal regulation and bone metabolism. The summary of selected phytochemicals is provided in Table II.

Table II: Overview of potential phytochemical for osteoporosis treatment.

Phytochemical / Scientific Name	Bioactive Compound	Therapeutic properties	Prevention or Treatment on osteoporosis	Role in osteoporosis	Tested model	References
Tongkat Ali *Eurycoma longifolia*	Quassinoids, β-carboline alkaloids, eurypeptides, phenolic compounds, glycoproteins	Enhances testosterone, osteoblast proliferation, induces osteoclast apoptosis Antimalaria, anticancer	Treatment	• Increases testosterone • Stimulates osteoblast proliferation • Induces osteoclast apoptosis • Maintains bone calcium levels	• *E. longifolia* extract stimulated the deposition of collagen and calcium in MC3T3-E1 cells • Sprague-Dawley supplemented with quassinoid-rich *E. longifolia* reduced osteoclasts and increased osteoblasts • Orchidectomised rats supplemented with *E. longifolia* prevented bone calcium	(16-21)
Kacip Fatimah *Labisia pumila*	Flavonoids, phenolic compounds, anthocyanins, β-carotene	Estrogenic, antioxidant, anti-inflammatory	Prevention	• Acts as oestrogen replacement • Enhances osteoblast activity • Reduces oxidative stress • Normalises OPG/RANKL ratio	• Postmenopausal rats supplemented with *L. pumila* reduced oxidative stress and prevented bone loss. • *L. pumila* extract enhanced OPG levels, reduced RANKL levels, and affected the RANKL/OPG ratio in postmenopausal rats model.	(22-28)

CONTINUE

Table II: Overview of potential phytochemical for osteoporosis treatment. (CONT.)

Phytochemical / Scientific Name	Bioactive Compound	Therapeutic properties	Prevention or Treatment on osteoporosis	Role in osteoporosis	Tested model	References
Daun Kaduk *Piper sarmentosum*	Naringin, quercetin, flavonoids, alkaloids, phenolic compounds (gallic acid, caffeic acid)	Anti-inflammatory, antioxidant, bone formation	Prevention	• Enhances osteoblast differentiation • Increases ALP activity • Promotes bone formation	• *P. sarmentosum* extract reduced the cell division cycle and promoted ALP activity in hPBSc • *Ethanolic P. sarmentosum* extract enhanced ALP enzyme activity, increased and mineralised the expression levels of osteoblast markers (Runx2, OCN and OPN) in hPBSc	(27-31)
Herba Epimedii	Icariin, flavonoids, sagittatoside, quercitrin, hyperoside, astragalin	oestrogenic, bone strengthening, antioxidant	Prevention and Treatment	• Promotes bone formation • Inhibits osteoclastogenesis • Increases osteoblast markers (Runx2, ALP, OCN) • Reduces oxidative stress	• *H. epimedii* extract administered to diabetic rats promoted bone formation and reduced oxidative stress in the bones • *Epimedium prenylflavonoids* increased BMD and peak bone mass in animal models and post-menopausal women	(32-38)
Soybean *Glycine max*	Isoflavones (genistein, daidzein), omega-3-fatty acids, peptides, phytosterols	anticancer, antioxidant, antibacterial, anti-inflammatory, antiviral, antidiabetic	Prevention and Treatment	• Promotes osteoblast differentiation, • Inhibits osteoclastogenesis • Maintains bone density through oestrogen-like effects	• Induction of genistein in calvaria osteoblasts protected and increased bone through osteogenesis-associated gene expressions • genistein was found to support cell growth and osteoblast differentiation in osteoblasts • Daily intake of genistein over 24 months led to an increase in BMD, levels of IGF and ALP in the post-menopausal women	(24, 33, 35-37, 40-46)
Psoralea corylifolia	Psoralen, corylin, bakuchiol	Estrogenic, antioxidant, anti-osteoporotic	Prevention and Treatment	• Promotes osteoblast proliferation • Increases calcium deposition • Enhances osteoblast markers (Runx2, collagen type 1)	• Psoralen boosted Osx expression, regulated BMP-2 and BMP-4 gene expression in murine calvarial osteoblasts • Psoralen enhanced proliferation of cell, ALP activity and calcium deposition in hBMSCs • Corylin increased ALP activity and protein expression of osteoblast marker Runx2, collagen type 1 as well as deposition of calcium and OPG/RANKL on osteoblasts from rats	(47-53)

1 Pre osteoblasts cells
2 Osteoprotegerin
3 nuclear factor kappa-β ligand
4 Alkaline phosphatase
5 human peripheral blood stem cells
6 osteocalcin
7 osteopontin
8 Bone mass density
9 insulin-like growth factor

Tongkat Ali (*Eurycoma longifolia*)

Tongkat Ali, or Eurycoma longifolia, is a widely recognized herbal remedy in Southeast Asia, classified within the Simaroubaceae family. For many years, its roots have been employed across Asia to address various symptoms and ailments. Recently, *E. longifolia* has gained significance in Western herbal medicine as a supportive and alternative therapy. Traditionally, it has been utilised to treat intermittent fevers associated with malaria, high blood pressure, diarrhoea, sexual dysfunction, fever, enhancing energy, strength, as well as exercise recovery. This usage continues today as the root with regard to *E. longifolia* is believed to possess medicinal properties that boost male fertility as well as attractiveness, given its aphrodisiac qualities aimed at stimulating male sexuality (14). The *E. longifolia* is rich with variety types of bioactive compounds includes quassinoids, β-carboline alkaloids, canthin-6-one alkaloids, triterpene-type tirucallane, squalene derivatives, and eurycolactone, eurycomalactone, laurycolactone,

biphenyl neolignan and bioactive steroids (14,15). Other than that, *E. longifolia* also contain eurypeptides which stimulate dehydroepiandrosterone (DHEA) besides facilitating the conversion of androstenediol as well as androstenedione to oestrogen and testosterone through androgen receptors beside these eurypeptides may lower sex hormone binding globulin (SHBG), thereby increasing free testosterone levels. Furthermore, *E. longifolia* has a pro-androgenic effect that raises testosterone levels and promotes osteoblast proliferation while inducing osteoclast apoptosis. The water-soluble extract of *E. longifolia* comprises phenolic compounds, high-molecular-weight polysaccharides, tannins, glycoproteins, as well as mucopolysaccharides, which are believed to be the active biological components regulating bone calcium levels (14,16).

In the review done by Mohd Effendy et al., *E. longifolia* is an alternative treatment concerning male osteoporosis caused by androgen deficiency, enhancing testosterone levels and maintaining bone remodelling activity without the side effects of testosterone replacement therapy (17). It is supported by study done by Thu et al. in preosteoblast cells (MC3T3-E1 cells), an *in vitro* model. The *E. longifolia* extract at 25 µg/ml is optimum concentration for the MC3T3-E1 cells stimulated the mineralisation of bone (collagen synthesis and calcium deposition) after 21 days (18). Consequently, it demonstrates a greater potential for enhancing osteoblast proliferation and differentiation compared to testosterone, positioning it as a viable alternative for testosterone replacement therapy with regard to the treatment of male osteoporosis. In different study on animal study done by Jayusman et al., *E. longifolia* supplemented in degarelix-induced showed that quassinoid-rich *E. longifolia* was as efficient as testosterone against androgen deficient-bone structural changes, particularly for the chemical castration model (19). Apart from that, orchidectomised rats supplemented with *E. longifolia* observed able to maintained osteocalcin (OCN) concentration, collagen type 1 and fourth lumbar bone calcium after 6 weeks of treatment compared to orchidectomised rats. *E. longifolia* effectively prevented bone calcium loss with regard to orchidectomised rats, indicating its potential as an alternative treatment concerning osteoporosis resulting from androgen deficiency (16).

Kacip Fatimah (*Labisia pumila*)

Labisia pumila, known as Kacip Fatimah, is a notable herbal treatment in Asia, originating from the Myrsinaceae family. Traditionally, Malay women have employed *L. pumila* water extract to remedy menstrual problems and dysmenorrhea, facilitate uterine contractions postpartum, and improve sexual function. This water extract is also utilised in the treatment of gonorrhoea, rheumatism, diarrhoea, and bone problems. This plant is abundant in bioactive substances, including beta-carotene, flavonoids, phenolic compounds, and anthocyanins, which have oestrogenic and antioxidant qualities that are good for bone health (20). Research has indicated that the plant extract from *L. pumila* possesses estrogenic properties, acting as oestrogens receptor modulators in postmenopausal women. Furthermore, the water extracts have shown to displace antibody binding and elevate anti-oestradiol antibodies, making them comparable to other oestrogens, including estrone and oestradiol (21). Postmenopausal women are at risk of contracting osteoporosis due to reduced circulation with regard to oestrogen hormones. Note that oestrogen facilitates apoptosis in osteoclasts while inhibiting it in osteoblasts, thereby slowing bone degradation and promoting bone formation. Hence, it indicates that *L. pumila* can induce the release of oestrogen (22). Supplementation with *L. pumila* at doses of 20 mg/kg as well as 100 mg/kg demonstrated optimal outcomes at 9 weeks, potentially reducing oxidative stress and preventing bone loss in rats with postmenopausal osteoporosis through its antioxidant properties (23). This study was supported by different study which use 17.5mg/kg of *L. pumila* extract daily for 8 weeks may be as efficient as oestrogen replacement therapy (ERT) in preventing fractures caused by oestrogen-deficient osteoporosis, offering an alternative treatment option (24). Therefore, *L. pumila* can be utilised as ERT due to its antioxidant properties derived from active compounds like anthocyanin, ascorbic acid, flavonoids, beta-carotene, as well as phenolic compounds present in the plant. In addition to its antioxidant as well as anti-inflammatory properties, *L. pumila* includes other active constituents, for example, anthocyanin as well as phenolics. Here, these effective free radical scavengers may assist in the treatment with regard to chronic diseases associated with oxidative stress (25). Furthermore, another study indicated that *L. pumila* extract enhanced osteoprotegerin (OPG) levels, reduced nuclear factor kappa-β ligand (RANKL) levels, and affected the RANKL/OPG ratio, although these changes did not achieve statistical significance. This suggests that the active ingredients in *L. pumila* may inhibit bone loss mechanisms by normalising OPG and RANKL levels (26).

Daun Kaduk (*Piper sarmentosum*)

Piper sarmentosum is an herbal plant commonly spotted in Malaysia, often utilised in traditional cuisine. Locally known as 'daun kaduk,' it is utilised for treating common ailments such as toothaches and flu-like symptoms, including headaches, asthma, coughs, and fever. This herb is rich in bioactive compounds such as flavonoids such as naringin, hesperidin and quercetin, phenolic compound includes gallic acid and caffeic acid, alkaloids and essential oil and exhibits various potential therapeutic properties, including anti-tuberculosis, hypoglycaemic effects, anti-cancer, anti-atherosclerosis, anti-malarial, antioxidant, and anti-inflammatory activities (27). Additionally, the flavonoids in *P. sarmentosum* can enhance osteoblast differentiation by increasing the expression of OPG which promotes bone formation. Moreover, *P. sarmentosum* has been shown

to enhance the dehydrogenase activity with regard to the 11β-hydroxysteroid dehydrogenase type-1 (11β-HSD1) enzyme as well as reduce the effects of corticosterone, which is crucial for regulating corticosteroid activity (25). In other research, the aqueous extract of *P. sarmentosum* leaves may enhance bone growth, indicating its potential as an alternative treatment for osteoporosis as well as osteoporotic fractures in patients receiving long-term glucocorticoid therapy. Specifically, the application of 1 µg/ml of *P. sarmentosum* extract in various studies showed the greatest potential to trigger the differentiation process in cells, thereby reducing the cell division cycle while promoting alkaline phosphatase (ALP) activity in human peripheral blood stem cells (hPBSc) (28). Furthermore, the advantages of *P. sarmentosum* were corroborated by another study, which found that a concentration of 50 g/mL of *P. sarmentosum* ethanolic extract enhanced ALP enzyme activity, increased the expression levels of osteoblast markers, for example, Runt-related transcription factor 2 (Runx2), OCN, and osteopontin (OPN), and promoted mineralisation in hPBSc, suggesting significant properties for inducing osteoblast differentiation (29).

Herba epimedii

In China, herbal plants from the Epimedium family are utilised for bone treatment. One species in this genus is Herba epimedii. In Chinese Herbal Medicine, elderly individuals use *H. epimedii* to tonify the kidneys as well as enhance bone strength (30). Additionally, the aqueous extract of *H. epimedii* is employed to prevent bone loss, containing numerous active compounds such as epimedin, baohuoside, sagittatoside, quercitrin, hyperoside, icariin, as well as astragalin (31,32). These bioactive compounds contribute to improved bone health and cardiovascular function, modulate immune responses, regulate hormone levels, and inhibit tumour growth. Due to its complexity, *H. epimedii* has been the subject of various studies, which includes those on anti-osteoporosis effects, oestrogen-like activity, and anti-tumour properties in both cell culture and animal models. *H. epimedii* treatment significantly influenced the differentiation with regard to rat bone marrow-derived mesenchymal stem cells (BMSCs), yielding elevated levels of Runx2, bone sialoprotein (BSP) mRNA, bone morphogenetic proteins (BMP), OPN, as well as OCN, while also decreasing peroxisome proliferator-activated receptor 2 (PPAR2) mRNA levels. Furthermore, it enhanced alkaline phosphatase (ALP) activity and reduced the number of adipocytes (33,34). The study administered *H. epimedii* at a dose of 300 mg/kg/day once a day for 35 days to diabetic rats treated with Rosiglitazone. This therapy plan led to a significant decrease in fasting blood sugar levels and a rise in serum insulin levels in the diabetic rats. The results indicate that treating diabetic rats with *H. epimedii* at this specific dose and duration can prevent bone loss by promoting bone formation and reducing oxidative stress in the bones (35). In different study on *Epimedium prenylflavonoids* which is active compound in *H. epimedii* positively affect osteoporosis by promoting bone cellular function, enhancing ALP levels, and suppressing osteoclastogenesis through the reduction of tumour necrosis factor receptor associated factor 6 (TRAF6) protein levels. They have been shown to increase bone mineral density and peak bone mass in animal models and post-menopausal women. Overall, these compounds may help prevent bone loss associated with menopause (36).

Soybean

Soybean (*Glycine max* L.) derived from the *Fabaceae* family is known as a legume that originated in southwest Asia and is broadly cultivated in warm climates. As a leguminous plant, soybean acts as functional food due to its high nutrient (34,37,38). It emerged as a viable food due to presence of bioactive compound that enhancing health such as omega-3-fatty acids, lectins, trypsin, inhibitors, peptides, saponins, phytates, phytosterols, and isoflavones particularly genistein, daidzein, and glycitein (37). As a result, the food based from soybean has therapeutic properties such that anticancer, antioxidant, antibacterial, anti-inflammatory, antiviral, as well as antidiabetic effects in which could help disease related to various lifestyle like diabetes, obesity, osteoporosis, and cardiovascular diseases (33,37,39).

Soybean serves as a protein that supports osteogenic differentiation in BMSCs, induces osteoblastic differentiation and mineralisation in vitro, as well as inhibits adipogenic differentiation. Meanwhile, genistein, a key soy isoflavone, has been shown to offer various health benefits. This isoflavone exhibits bone oestrogenic activity by slowing bone deterioration and alters β-lymphopoiesis in the bone marrow without exerting an oestrogenic effect on the uterus. Therefore, genistein exerts dual effects on bone cells: it promotes osteogenic differentiation and maturation of BMSCs as well as osteoblasts, while simultaneously inhibiting osteoclast formation and bone resorption activity within the bone cell body (22,38). Soy flavonoids can modify the gene expression associated with metabolism in postmenopausal women. Additionally, they regulate cytokines, calciotropic receptors, growth factor, ALP, collagen type-1, as well as OCN, while preventing bone loss by stimulating oestrogen to produce OPG and osteoclastogenesis inhibitors through binding to RANKL (31,38). Moreover, as phytoestrogens, soy flavonoids exhibit an antiestrogenic effect with regard to oestrogen receptor alpha (ERα) and ER beta-dependent gene expression in the brain, including oestrogen-related behaviour (40). Genistein induction in calvaria osteoblasts at 100µM for 24 hours has been shown to protect bone through osteogenesis-associated gene expressions mediated by Erα, which also increases the expression of the ALP, Runx2, as well as OCN genes expression (41). Apart from that in a separate study, 10µm of genistein was found to support cell growth and osteoblast differentiation in osteoblasts isolated from the

calvaria with regard to rat pups. The genistein treatment led to the upregulation of osteoblastic genes such as Runx2, BMP-2, and OCN. Immunolocalisation of BMP-2 further confirmed the osteogenic potential of genistein. Moreover, cells exposed to genistein suppressed the development of multinucleated osteoclasts, as evidenced by Tartrate-resistant acid phosphatase (TRAP) staining and the decreased expression of cathepsin K (42).

The soy flavonoids greatly influence bone metabolism concerning postmenopausal women. Several studies have indicated that genistein might contribute to the prevention and treatment of osteoporosis due to its structural and functional similarity to 17β-oestradiol. In a clinical trial involving postmenopausal women, a daily intake of 54 mg of genistein over 24 months led to an increase in BMD, as well as elevated levels of insulin-like growth factor (IGF) and ALP in the patients (43). Aside from that, soybean isoflavones like daidzein as well as genistein have been shown to raise whole body BMD in situations where serum calcium levels are high, but to drastically lower BMD when levels are low. As a result, it was demonstrated that these soybean isoflavones tend to sustain whole BMD when calcium levels are high (44). Consequently, soybean promotes bone formation and maintains skeletal growth by regulating oxidative stress and inhibiting osteoclast formation in primary osteoblasts.

Psoralea corylifolia L.

Psoralea corylifolia L., belonging to the *Fabaceae* family, has been traditionally utilised to prevent fractures and treat bone and joint diseases. This plant contains bioactive compounds such psoralen, corylin, psoralidin, bakuchiol, and isobavachin, which has strong oestrogenic activity. Its fruits treat bone fractures, osteomalacia, and osteoporosis. In addition, *P. corylifolia* has a strong inhibitory impact on osteoclasts, promotes osteoblastic proliferation, lowers bone resorption, and is thought to have a variety of other medicinal qualities, such as anti-microbial, antioxidant, and anti-osteoporotic actions. (45,46).

While bakuchiol and the extract demonstrated oestrogenic activity in *in vitro* studies, they did not show uterotrophic activity or reduce postmenopausal bone loss. This was evident as they did not increase ALP, BMD, calcium concentration, serum E2 levels, or the gene expression of osteoblast markers like glucose transporter 3 (GLUT3), BSP, OCN, collagen type-1, Runx2, as well as osterix. Psoralen, derived from the fruit of *P. corylifolia,* has been determined to stimulate localised bone formation in vivo and enhance osteoblast differentiation in primary murine calvarial osteoblasts with regard to a dose-dependent manner. Additionally, it boosts Osx expression, a direct target of BMP signalling, regulates BMP-2 as well as BMP-4 gene expression, elevates the protein level of phosphor-Smad 1/5/8, including modulates BMP in a dose-dependent fashion. This compound shows promise as an anabolic agent for treating osteoporosis (47–49). In the present study, 1 μmol/l of psoralen was found to have the most potent effect on the osteogenic differentiation with regard to human bone marrow stem cells (hBMSCs), enhancing proliferation, ALP activity, and calcium deposition. It is suggested that psoralen aids in the binding of TGF-β to its receptor, TGF-β RI, subsequently triggering RI-mediated Smad3 signalling. Consequently, Smad3 becomes activated in the nucleus, initiating the transcription with regard to specific genes and promoting the differentiation concerning hBMSCs into osteoblasts. This process boosts osteoblast function and supports the mineralisation of the extracellular matrix (50). Other than psoralen, corylin is one of the flavonoid useful in *P. corylifolia*. The study conducted using corylin on primary osteoblasts derived from the calvaria of rats showed that 10μm of corylin increased ALP activity and protein expression of osteoblast marker Runx2 and collagen type 1. Beside that, it also promoted the deposition of calcium as proven by Alizarin Red staining and increased the OPG ratio to receptor activator with regard to RANKL mRNA expression (51).

TREATMENT OF OSTEOPOROSIS

EOsteoporosis can be treated using two approaches i.e. non-pharmacological and pharmacological. The pharmacological approach involves medications like bisphosphonates, denosumab, and teriparatide. On the other hand, non-pharmacological treatments include sufficient vitamin D as well as calcium supplementation, participation in weight-bearing exercises, quitting smoking, minimising caffeine and alcohol intake, and implementing fall-prevention measures. The comparison of the current and alternative treatment for osteoporosis is summarised in Table III.

Table III: Comparison on current treatment and phytochemical based therapies for osteoporosis.

Aspect	Current Pharmaceutical Treatments	Herbal/Phytochemical-based Therapies
Effectiveness and Approach	- Direct intervention (e.g., increasing bone density or slowing bone loss). - Effective but side effects present. - No drastic change in the long-term progression of bone complications.	- Focus on prevention and maintenance. - Used in traditional medicine for centuries. - More gradual and holistic approach.
Side Effects	- Significant side effects limit long-term use and effectiveness.	- Generally seen as gentler with fewer severe side effects. - Requires more clinical research to validate claims.
Research and Development	- Backed by extensive clinical trials and research. - More refined drug formulations.	- Limited research on mechanisms and efficacy. - Need for more bioassays and clinical trials to prove effectiveness.
Mechanism of Action	- Affects bone metabolism (e.g., reducing bone resorption or promoting bone formation).	- Mechanisms less understood. - Involves complex processes like the kidney-bone axis. - Potential for drug synthesis from plant compounds.
Potential and Limitations	- Immediate and measurable effects. - Constrained by side effects and limited long-term efficacy.	- Great potential as natural alternatives. - Limited by insufficient research and lack of clinical trials.

Pharmacological treatment

Regarding pharmacological treatment, antiresorptive agents like bisphosphonates, oestrogen agonists/antagonists (EAAs), oestrogen, calcitonin, denosumab, as well as anabolic agents such as teriparatide, are utilised to reduce fracture risk. The primary goal of antiresorptive drugs is to slow bone resorption. Apart from that, anabolic medications enhance bone formation instead of resorption. Although some medications have overlapping indications, not all osteoporosis treatments have received Food and Drug Administration (FDA) approval for use in postmenopausal women, men with osteoporosis, or those with glucocorticoid-induced osteoporosis (GIO) (3). Nonetheless, the American Association of Clinical Endocrinologists/American College (AACE/ACE) recommends bisphosphonates as well as denosumab as first-line therapies for postmenopausal women at high risk of fractures. For patients unable to consume oral medications, alternatives such as zoledronic acid, denosumab, or teriparatide may be recommended (52).

Bisphosphonates are analogues of inorganic pyrophosphate that help prevent bone loss related to aging by promoting apoptosis in osteoclasts, which in turn inhibits bone resorption. They are both effective and cost-effective, with extensive long-term safety data available. There are two categories of bisphosphonates: nitrogen-containing bisphosphonates (NBPs), like zoledronate and alendronate, which block the mevalonate pathway and hinder the maturation of osteoclast precursors into cells that resorb bone. On the other hand, non-nitrogen containing bisphosphonates (NNBs) like etidronate are metabolised to disrupt mitochondrial function to cause osteoclast apoptosis (53–55). Bisphosphonates are widely prescribed for osteoporosis particularly in postmenopausal men as well as women over 50 (3,55,56). Nevertheless, bisphosphonates should be avoided by patients whose impaired kidney function due to renal excretion (3). The negative effects of bisphosphonate consist of short-term Barrett's oesophagus and gastrointestinal issues, while the long-term effects encompass atrial fibrillation, renal failure, suppression of bone turnover, subtrochanteric femoral fractures, as well as jaw osteonecrosis (52,57).

Denosumab is endorsed by the AACE/ACE for patients at high fracture risk who cannot take oral medications. It is the first fully human monoclonal antibody that directly binds to RANKL, inhibiting bone resorption by blocking osteoclast formation and activation. The Food and Drug Administration (FDA) has approved denosumab for the treatment of osteoporosis in high-risk postmenopausal women and older men who have experienced a fracture, aiming to enhance their bone mass. It is widely accessible and effective (3,52,56). The side effects include severe infections, hypersensitivity, musculoskeletal discomfort, dermatological reactions, and hypercholesterolemia have been examined as side effects of denosumab, thus calcium levels should be observed prior to the treatment (3,58). Denosumab is eliminated from the bloodstream through the reticuloendothelial system and generally does not lead to the production of neutralising antibodies (59). However, the discontinuation can increase the risk of vertebral fractures, making continued therapy at a lower dose a potential strategy, though this requires further clinical trials (60,61).

Teriparatide refers to a recombinant human parathyroid hormone molecule consisting of the first 34 amino acids of the full-length parathyroid hormone (PTH, which has 84 amino acids). When administered intermittently via injections, it has an anabolic effect, increasing trabecular bone and improving cortical thickness and trabecular connectivity (62,63). Teriparatide is a safe and convenient option for promoting new bone tissue and can help correct structural defects in the osteoporotic skeleton. It is typically administered for 24 months in clinical trials (64). This treatment increases BMD by reducing approximately 70% with regard to vertebral fractures, as well as about 45% concerning non-vertebral fractures in postmenopausal women, even

though there is no evidence that it prevents hip fractures (62). The teriparatide stimulates osteoblasts, resulting in bone formation that exceeds resorption during the initial treatment stages. Additionally, teriparatide treatment may be associated with mild side effects, including nausea, upper gastrointestinal symptoms, dizziness, limb pain, hypercalcemia, headache, hypercalciuria, hyperuricemia, and hypotension (65,66). It significantly increases BMD with regard to the lumbar spine as well as femoral neck, but prolonged use beyond the recommended period may increase the risk of osteosarcoma, as suggested by preclinical animal studies (52,65).

Non-pharmacological treatment

To support bone health, it is recommended by the Institute of Medicine (IOM) that individuals over 50 years old consume between 1000 and 1200 mg of calcium on a daily basis, ideally from dietary sources. If dietary calcium is inadequate, supplementation may be necessary; however, it should not exceed 1200 mg daily, with doses limited to 500–600 mg at a time for optimal absorption (3,67). Excessive calcium intake can lead to hypercalcemia and increase kidney stones, particularly in those who supplement rather than rely on dietary sources (68,69).

Vitamin D is also suggested for osteoporosis since it enhances calcium absorption and supports bone health. Moreover, the IOM advises a daily intake of 600 to 800 International Units (IU) for individuals over 50 years old (3). While vitamin D supplementation reduces fracture risk, excessive intake may increase the risk of falls. Consequently, it is advisable to regularly prescribe lower doses of vitamin D. However, Vitamin D alone is not sufficient for the treatment or prevention of osteoporosis. Therefore, combining calcium with vitamin D is recommended. Calcium is absorbed in the intestine through a vitamin D-dependent active transport mechanism as well as passive diffusion. Given that calcium absorption is inversely related to dietary intake, the active transport mechanism plays a crucial role in maintaining calcium homeostasis (52). Additionally, vitamin D facilitates calcium homeostasis and regulates parathyroid hormone levels by enhancing the intestinal absorption of dietary calcium and enhancing proximal muscle function, especially in cases of deficiency. Moreover, vitamin D increases osteoblastic activity, and for older adults at high risk, a deficiency may accelerate the progression of osteoporosis. In contrast, oestrogen deficiency after menopause primarily impacts trabecular bone and is influenced by changes in osteoclastic activity (70,71).

Lifestyle modifications are essential for reducing fracture risk, with key steps including limiting alcohol and caffeine intake and quitting smoking. Recently, coffee drinking has become a popular trend among working individuals, particularly those over 25. High consumption with regard to alcohol and caffeine is related to lower BMD and a greater risk of osteoporosis (72–74). Smoking especially in the long term reduce BMD and negatively impacts bone health due to nicotine's effects on osteoblasts, leading to reduction bone formation (75–77). Engaging in physical activities like walking and jogging is vital for both preventing as well as treating osteoporosis. These activities help minimise the risk of fractures (spine and hip) and promote the formation of new bone at stressed skeletal areas, and especially in athletes (78,79).

CONCLUSION

The conclusion of the paper emphasises the importance of understanding osteoporosis as a multifactorial disease that requires a comprehensive approach to prevention and treatment. It highlights the potential of phytochemicals derived from natural sources as effective alternatives or adjuncts to conventional therapies. The review suggests that while traditional treatments are beneficial, integrating natural compounds may enhance therapeutic outcomes and reduce side effects. The authors advocate for further research to validate the efficacy and safety of these natural agents in managing osteoporosis, ultimately aiming to improve patient care and quality of life.

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