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Review

Asian plants as a promising alternative to classic drugs in postmenopausal osteoporosis: A review of literature from clinical perspective

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Osteoporosis is characterised by low bone mineral density (BMD) resulting in fragile bones with increased risk of fracture. According to statistics, 75 million people worldwide suffer from osteoporosis. However, the higher consumption of soy by the Asian population is thought to be one of the contributing factors for the lower incidence of osteoporosis-related fractures in the region. Various side effects were reported to be associated with the use of both estrogen or hormone replacement therapy, and other classical anti-fracture agents. Therefore, alternative approaches, and especially natural therapies to treat osteoporosis are currently under research. In traditional Chinese medicine, osteoporosis is considered to be a disorder caused by the insufficiency of kidney yang, and the herbs perceived to be able to tonify the kidney yang have been used for more than 1000 years as therapy. Within this context, we have systematically researched the specialty literature on the topic, in an attempt to check whether various Asian plants could constitute valid therapies in the prophylaxis and treatment of osteoporosis, especially postmenopausal one. The current evidence suggests that isoflavones as well as other compounds from Asian plants extracts may regulate bone turnover by complex mechanisms and increase BMD, thus, potentially, reducing the fracture rate.

Key words: Osteoporosis, traditional Chinese medicine, Asian plants, bone turnover, osteoclast, osteoblast, estrogen, postmenopause.

INTRODUCTION

Osteoporosis is the most common metabolic bone disorder and an important health care issue in both Caucasians and Asians, extremely likely to aggravate with aging populations around the world. Although osteoporosis commonly affects both older men and women, postmenopausal women represent the primary focus of the disease. Women's Health Initiative Study as well as The Million Women Study indicated that long-term estrogen or hormone replacement therapy (HRT) in postmenopausal women may enhance the risk of breast cancer, stroke, thrombosis and cardiovascular disease, even though significantly reducing vertebral and non-vertebral fracture risk (Rossouw et al., 2002; Beral et al., 2003). These findings pointed out against the use of HRT as first-line therapy for the prevention and therapy of postmenopausal osteoporosis. As various side effects were reported to be associated with the use of other anti-fracture agents such as bisphosphonates, selective estrogen receptor (ER) modulators, human parathyroid hormone-derived peptides and calcitonin (Papaioannou et al., 2007), alternative approaches and natural therapies in the management of osteoporosis have become worth exploring.

Phytoestrogens are considered to be an effective

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option in preventing bone loss caused by the deficiency of either estrogen and/or androgen. The higher consumption of soy by the Asian population is thought to account for the lower incidence of osteoporosis-related fractures in the region (Glazier et al., 2001) and data from both human and animal studies using soy isoflavones sustain the hypothesis that a diet high in soy exerts beneficial effects on bone health (Arjmandi et al., 1996; Picherit et al., 2001; Chen et al., 2003).

Mounting evidence shows positive effects of Chinese herbal drugs as primary or adjuvant treatment in human diseases. To exemplify, in chronic viral hepatitis C, antiviral treatment is associated to partial response and several adverse effects (Duncea and Pepene, 2008); nonetheless, randomized clinical trials reported improved virological response after interferon plus Chinese herbs compared to interferon alone (Zhao et al., 2011). In traditional Chinese medicine (TCM), osteoporosis is considered to be a disorder caused by the insufficiency of kidney yang; thus, herbs such as Fructus Ligustri Lucidi (Nv-Zhen-Zi), Hominis Placenta (Zi-Hec-Che), Herba Epimedii (Yin-Yang-Huo) and Rhizoma Drynariae (Gu-Sui-Bu), thought to invigorate the kidney yang, have been used for more than 1000 years for the therapy of osteoporosis (Ma et al., 2011b; Zhang et al., 2010b). In addition, various Kampo medicines (i.e., Hachimijiogan, Juzentaihoto and Unkeito) were indicated to be useful for preventing postmenopausal osteoporosis (Hidaka et al., 1997; Hattori et al., 2010).

In this context, the purpose of this review is to present and assess recent studies on the effects of several Asian plant extracts on bone turnover, bone mineral density (BMD) and bone health and discuss the potential mechanisms involved in their action.

THE GENUS EPIMEDIUM

Herba Epimedii is one of the most commonly used Chinese herbs in the prevention and treatment of osteoporosis in TCM. *Epimedium* (*Berberidaceae*), also known as Rowdy Lamb Herb, Barrenwort, Bishop's Hat, Fairy Wings, Horny Goat Weed, Xianlinpi, Yangheye and Yin Yang Huo (Chinese: 淫羊藿) is a genus of about 52 species of herbaceous plants of which more than 15 species are believed to help “nourishing the kidney and reinforcing the Yang”. The crude extracts and compounds from the aerial parts or roots have various biological functions . According to the literature, the high content of flavonoids and polysaccharides in *Epimedium* plants, Wang and Liu (2008) especially 8-prenylflavonoids, account for most of its pharmacological activities. *In vivo* and/or *in vitro* experiments demonstrated that *Epimedium* and its active compounds such as icariin, icaritin, desmethylicaritin, des-methylanhydroicaritin, icariside II, ikarisoside A, baohuoside-1, baohuoside II, epimedokoreanin B, breviflavone B, luteolin, hyperoside, epimedin B or epimedin C benefit from wide-reaching pharmacological actions such as anti-oxidative, anti-tumor and anti-aging effects, and modulators of immunological functions (Ma et al., 2011a).

Effects on proliferation and differentiation of bone-forming cells

The crude extract, total flavonoids and main flavonoid constituents from *Herba epimedii* have been shown to stimulate the proliferation of primary osteoblasts (Wang et al., 2002; Han et al., 2003; Meng et al., 2005; Zhang et al., 2008a) and osteoblast-like UMR106 cells (Meng et al., 2005; Xie et al., 2005). At concentrations of 1–10 mg/l, the total flavonoids of *Epimedium pubescens* significantly augmented the number of osteoblasts and intensified mineralized tuberculation *in vitro* (Li et al., 2002b). *H. epimedii* extract has been shown to limit bone loss in an ovariectomized (OVX) rat model (Chen et al., 2011) by increasing cell proliferation and intensifying alkaline phosphatase (ALP) activity in primary rat calvarial osteoblasts (Li et al., 2002b; Han et al., 2003; Zhang et al., 2008a; Chen et al., 2009; Songlin et al., 2009). A recent study also proved that *Epimedium wushanense*, a common type of *H. epimedii,* is able to stimulate osteogenic differentiation of human bone marrow-derived mesenchymal stem cells (Zhang et al., 2010a). The up-regulation on bone morphogenetic proteins (BMP) and *Wnt*-related regulators mRNA expression suggests involvement of both the BMPs- and *Wnt*-signaling pathways in *H. epimedii*-stimulated bone formation (Zhang et al., 2010a).

Polysaccharides from *Epimedium* determined significant growth of cell proliferation rates and DNA synthesis in cultured mouse bone-marrow cells (Liu et al., 1991). The serum from old male rats continuously fed with the water extract of *Epimedium* (1,2 g/ml) for one month increased the proliferation and differentiation of newborn rat calvarial osteoblasts, an effect possibly mediated by the generation of a relatively large number of bone formation mediators such as BMP and leptin (Ma et al., 2002b). Moreover, *Epimedium* has been proved to enhance gonadal hormones secretion and promote an androgen-like effect on the proliferation and differentiation of osteoblasts.

Further studies showed that various doses of icariin, the major flavonoid compound in *H. epimedii,* increase the proliferation and activity of cultured osteoblasts. Especially at a dose of 10 ng/ml, icariin had a depressive effect on ALP activity in the early stage while enhancing ALP activity in the later stage of osteoblast maturation (Wang et al., 2002). Notably, there seems to be a relationship between osteoporosis and trace-element deficiency and the efficacy of calcium (Ca), manganese (Mn) and zinc (Zn) supplementation on spinal BMD in postmenopausal women. Mineral elements such as

manganese , zinc and iron (Fe) appear surprisingly abundant in *H. epimedii*. In line with these data, the combination of Zn, Ca and Mn with icariin and total flavonoids significantly improves cell viability and intensifies ALP activity compared to each agent alone (Zhang et al., 2008a,b,c).

Effects on osteoclastic cells metabolism

When an *Epimedium* solution is parenterally administered, it promotes osteoclast apoptosis and inhibits bone resorption in a dose-dependent manner (Li et al., 2002a). *In vitro,* total flavonoids (10^{-4} mol/l) of *H. epimedii* reduced the number of osteoclasts and directly inhibited osteoclast resorption activity (Zhang et al., 2004). Further studies have proved that the inhibitive effects of flavonoids on the proliferation of the RAW 264.7 cell line are bidirectional, and depend on their concentration and chemical structures. Ikarisoside A inhibits osteoclastogenesis in nuclear factor-κappaB (NF-κB)-stimulated RAW 264.7 cells as well as in bone marrow-derived macrophages. In fact, expression of osteoclast-specific genes, such as matrix metalloproteinase-9, tartrate-resistant acid phosphatase, receptor activator of NF-κB (RANK) and cathepsin K is repressed by ikarisoside A (2.5–20 μM). These findings constitute an argument for possibly using ikarisoside A in the treatment of diseases involving abnormal bone lysis, such as osteoporosis, rheumatoid arthritis and periodontal bone erosion (Choi et al., 2010a).

In rabbit bone-marrow cells, icariin at concentrations of 100, 50 and 10 μmol/l significantly inhibited the bone-resorbing activity of osteoclasts and greatly reduced the number and surface area of resorption lacuna. Thus, icariin limits bone loss not only by suppressing the bone-resorbing activity of mature osteoclasts but also by reducing the formation of osteoclast-like multinucleated cells (Zhang et al., 2007a).

In UMR-106 cells, icariin mimicked 17β-estradiol in stimulating cell proliferation, ALP activity and osteoprotegerin (OPG)/RANKL mRNA expression via the ER suggesting that it could exert estrogen-like effects in promoting osteoblastic functions and inhibiting osteoclastogenesis (Xie et al., 2005; Zhang et al, 2007b). Mechanistic studies indicated that the oestrogenic effects of icariin on osteoblastic cells did not depend on estrogen responsive elements in the ER as icariin did not activate estrogen responsive elements-luciferase activity in UMR 106 cells, via the ERα- or the ERβ-mediated pathways and involved activation of the ER by rapid phosphorylation (Mok et al., 2010).

Human and animal studies

Oral administration of total flavonoid (TF) extracts of *Epimedium* to rats with osteoporosis significantly increasees increases the femur dry weight, femoral ash weight and the calcium and phosphorus contents of bone, augmenting the trabecular bone area and trabeculae thickness of the proximal tibia as well as the cortical bone area percentage in the middle section of the tibia (Ma et al., 2002a). The administration of a lyophilized aqueous extract of *Epimedium* to castrated male rats for 12 weeks significantly increased serum OPG concentration and BMD, and decreased the microcrack percentage per unit trabecular area. *Epimedium* prevented the loss of bone mass and improved bone structure in castrated male rats (Wang and Liu, 2008). Intragastric administration of 5 g/(kg day) *Epimedium* to male rats with Kidney-Yang insufficiency induced by prednisone intensified bone formation and helped rebuild the injured bone by increasing the serum BMP-7 content and up-regulating renal and femoral BMP-7 expression (Zhou et al., 2008).

As proved by Zhang et al. (2007b), a preparation containing 60 mg icariin, 15 mg daidzein and 3 mg genistein was able to decrease bone loss in late postmenopausal women in a 24-month randomized, double-blind and placebo-controlled trial. The increase in vertebral and femoral neck BMD in the icariin-treated group was accompanied by suppression of urinary deoxypyridinoline levels, thus, suggesting that the bone-protective action of icariin is mediated by suppression of bone resorption.

More recently, Chen et al. (2011) described the dose-dependent effects and mechanisms of action of the TF fraction of *H. epimedii* extract on bone and mineral metabolism in OVX mice, showing that TF suppressed OVX-induced increase in urinary Ca excretion as well as loss of bone mass and strength at the distal femur in mice in a dose-dependent manner. It augmented total BMD and trabecular BMD of the distal femur in OVX mice, with the most effective dosages at 50-100 μg/g. In that study, there was an inverse correlation between the changes in urinary Ca excretion and the expression of renal Ca transport protein (CaBP-28K) and vitamin D receptor mRNA, which suggests for the first time that TF exerts additional effects on CaBP-28K m RNA expression in the kidney that may contribute to bone mass preservation in OVX mice. In addition, TF treatment increased type I collagen and osteocalcin (OC) mRNA expression and the OPG/receptor activator of NF-κB ligand (RANKL) mRNA ratio, and suppressed the growth in interleukin (IL)-6 mRNA induced by OVX in the femur of mice. The results indicated that the increase in the OPG/RANKL ratio by TF was different from that of estradiol and can be accounted for by its inductive effects on OPG mRNA expression, *in vivo.* In OVX rats, icariin augments the mRNA expression ratio of OPG/RANKL in tibia, following OVX (Mok et al., 2010). These results confirm the ones of a previous animal study (Xie et al., 2005) in which the extracts of *H. epimedii* increased trabecular BMD in OVX rats and also induced the expression of OPG mRNA and OPG/RANKL ratio, all

these suggesting that it could modulate the process of osteoclastogenesis. It should be mentioned that icariin lacks uterotrophic effects.

ISOFLAVONES

Soy isoflavone preparations, such as purified genistein and a soy extract (Novasoy®), have been proved to exert beneficial effects on bones. Genistein has been extensively studied as one of the main phytoestrogens. Due to its structure and the fact that it resembles 17β-estradiol, genistein can compete with estradiol for the ER (Ma et al., 2011b). Various studies using cultured bone cells, OVX rat models and clinical trials supported the fact that genistein might provide an alternative to prevent postmenopausal bone loss (Ullmann et al., 2005; Atmaca et al., 2008). In a randomized, double-blind, placebo-controlled trial that enrolled 389 postmenopausal women with osteopenia, it was shown that genistein enhanced BMD by increasing urinary excretion of pyridinoline and deoxypyridinoline and increasing alkaline phosphatase and serum insulin-like growth factor (IGF)-1 levels (Marini et al., 2007). Apart from the systemic circulation, IGF-1 is abundantly found in both trabecular and cortical bone (Pepene et al., 2004a,b) to directly or indirectly mediate the effects of estrogens, parathyroid hormone, growth hormone and thyroid hormones (Pepene et al., 2001, 2003) and glucocorticoids (Pepene et al., 2010) on bone cells metabolism. To support isoflavones positive effects on bone *via* the IGF-1/IGF-1R pathway, it was reported that isoflavones extracted from *Sophorae fructus*, (Isocal®) are able to up-regulate the growth factors IGF-1 and transforming growth factor-ß in rat bone marrow cells (Joo et al., 2004).

Novasoy® is a commercial isoflavone-enriched product that contains 40% isoflavones and 60% other naturally occurring soy proteins. The effects of genistein and Novasoy® on tri-dimensional trabecular bone parameters and the expression of bone-specific genes in OVX mice were compared for the first time by Zhang et al. (2009), to conclude that the diet containing soy extract in the form of Novasoy® was more effective in improving trabecular BMD and micro-architecture of the tibia in comparison to the diet containing purified genistein. Other bone-active soy isoflavones such as daidzein and glycitein are also found in Novasoy®, and this might account for the different effects of the two isoflavones in the OVX rat (Picherit et al., 2000; Somjen et al., 2008). Additionally, purified genistein decreased RANKL-, carbonic anhydrase II- and cathepsin K-mRNA expression and increased the OPG/RANKL-mRNA ratio in the tibia head of OVX mice, whereas Novasoy® stimulated OPG mRNA expression but had no effect on the OPG/RANKL-mRNA ratio (Zhang et al., 2009) thus suggesting that the two drugs exert distinct actions on osteoclastogenesis. Nevertheless, further studies are needed to confirm the bone protective effects of genistein and Novasoy in humans.

Comparative studies on the ability of the two well-known phytoestrogen compounds, genistein and icariin to enhance differentiation and mineralization of cultured rat calvarial osteoblasts concluded on that, compared to genistein, icariin has a stronger effect, as demonstrated by ALP activity, OC secretion, calcium deposition and the number and area of mineralized bone nodules. The same applies for its ability to stimulate the gene expression of type 1 collagen α2, BMP-2, osterix (OSX), and Runx-2 (Ma et al., 2011b); the prenyl group on C-8 of icariin could play the active role in osteoblastic differentiation, and this may explain why icariin is more potent than genistein in stimulating differentiation of osteoblasts. However, they inhibited proliferation of osteoblasts to a similar degree (Ma et al., 2011b).

FRUCTUS LIGUSTRI LUCIDI

The source of the crude drug, fructus ligustri lucidi (FLL, Chinese name, Nvzhenzi) is the fruit of *Ligustrum lucidum*. In the OVX rat, FLL increases the calcium absorption rate and improves calcium balance as well as BMD in both sham- and OVX rats, thus, suggesting that the actions of FLL on bone might differ from other phytoestrogen-containing plants (Zhang et al., 2008d). Treatment of UMR-106 cells with FLL extracts increases the formation of calcified matrix and intensifies extracellular calcium and phosphorus depositions in time- and dose-dependent manner. The enhanced mineralization may, at least partially, explain the increase of cortical bone mass in the appendicular skeleton by promoting new bone formation. Recently, Li et al. (2010) showed that the ethanol extract of FLL significantly enhanced ALP activity, reduced the time needed for the mineralization of bone marrow stromal cells and increased the expression of several osteoblast differentiation regulators such as BMP-2, OPG and ß-catenin. Overall, these effects support the hypothesis that FLL improves calcium balance and stimulates osteoblastic differentiation to promote bone formation.

DIPSACUS ASPER WALL

Dipsacus asper wall (DAW), belonging to *Dipsacaceae*, is a kind of perennial herb growing in moist fields and mountains. In a rat study, DAW increased bone density and improved bone histo-morphology (Liu et al., 2009). Several chemical constituents, in particular *Dipsacus* saponins, have been extracted from the root of DAW. Preliminary experiments showed that three of them, namely, Asperosaponin (ASA) acetyl, ASA IV and ASA VI, could stimulate cell proliferation in MC3T3-E1 osteoblasts, with the ASA VI displaying the most potent effect. In line with these data, Niu et al. (2011) recently demonstrated that the treatment of MC3T3-E1 and primary

rat osteoblasts with ASA VI not only promoted proliferation and increased ALP activity but also stimulated bone nodules formation. The possible mechanism is that ASA VI induces osteoblast maturation and differentiation, and then increases bone formation via intensified BMP-2 synthesis, and activating p38 and extracellular signal-regulated kinase (ERK) 1/2.

Acanthopanax senticosus

Acanthopanax senticosus (AS), also called Siberian ginseng, is a widely used oriental herb that has been reported to exert immunomodulatory, hypoglycemic, anti-stress, anti-tumor, anti-allergic and anti-oxidant effects. It was reported that AS contains various flavonoids such as quercetin, quercitrin, rutin, and hyperin. Wattel et al. (2004) demonstrated that quercetin may inhibit osteoclastic differentiation, *via* a mechanism involving NF-κB and activator protein-1 (AP-1). Another group reported that quercetin has a stimulatory effect on osteoblastic activity through ERK- and ER pathway (Prouillet et al., 2004). Furthermore, in a 6-month, prospective randomized study, Hwang et al. (2009) investigated the effects of AS extract on biochemical markers of bone turnover and BMD in 81 Korean postmenopausal women with low bone mass aged less than 65. No significant changes in BMD were observed; nevertheless, the study showed that a 6-month treatment with AS extract may have a favorable effect on bone remodeling in women with reduced BMD, increasing serum OC by 23.3% and decreasing serum C-telopeptide by 8.2%.

Paeonia lactiflora Pallas

Numerous studies have indicated that inflammatory cytokines play a major role in osteoclastogenesis, promoting bone resorption. Paeonol (2′-hydroxy-4′-methoxyacetophenone) is the main active compound of the *Paeonia lactiflora Pallas*, a traditional Chinese herb. Paeonol has an anti-inflammatory effect, suppressing cyclooxygenase-2, nitric oxide synthase, cell surface adhesion molecules, IL-1β and tumor necrosis factor (TNF)-α genes expression and inhibiting the activity of ERK and p38 (Nizamutdinova et al, 2007). In the study by Tsai et al. (2008), paeonol was shown to inhibit not only osteoclastogenesis from bone marrow stromal cells and macrophages via attenuated RANKL-induced ERK, p38 and NF-κB activation but also the resorption activity of mature osteoclasts. Additionally, paeonol prevented bone loss induced by ovariectomy *in vivo*.

FRUCTUS CNIDII

Osthole, one of the main components of the dried seeds from the Fructus Cnidii (FC) plant was reported to exhibit estrogen-like effects, preventing osteoporosis in OVX rats (Li et al., 2002c). However, the bone-forming actions of FC on osteoporosis and the biological effects of osthole on bone cells are relatively unknown. Kuo et al. (2005) reported osthole-mediated cell differentiation through the BMP-2, p38 and ERK1/2 pathways in human osteoblast cells. Furthermore, enhanced cell proliferation and differentiation was demonstrated in osthole-treated osteoblasts isolated from neonatal Sprague-Dawley rat calvaria (Zhang et al., 2010b).

SAIKO-KA-RYUKOTSU-BOREI-TO

Several studies have shown that statins, which are drugs with lipid-lowering effects, also have potentially beneficial effects on bone metabolism. Saiko-ka-ryukotsu-borei-to (SRB) is a traditional Japanese herbal medicine used to treat hyperlipidemia and inhibit aortic intimae thickening in hypertensive patients. Hattori's group investigated the effect of SRB on bone metabolism using an OVX murine model and showed that the bone volume of the proximal tibia of SRB-treated mice is significantly greater than that of mice in the OVX group, as assessed by micro-CT, and that the protective effects of SRB on bone in OVX mice are explained by the suppression of bone resorption. The study also shows that levels of serum IL-6, a primary mediator of bone resorption, were significantly lower in the SRB group compared to the OVX group, thus, suggesting that SRB may suppress osteoclastogenesis by decreasing serum IL-6 level (Hattori et al., 2010).

Achyranthes bidentata

Using the bone organ culture system, He et al. (2010) demonstrated that *Achyranthes bidentata* (AB), another Chinese herbal drug shows potent inhibitory activity on PTH-induced bone resorption. Further research using the OVX rat model revealed that AB significantly prevented BMD loss without any estrogen-like side effects. The main active chemical constituents are oleanolic acid glycosides, ecdysone type compounds and allantoin. Oleanolic acid glycosides inhibit osteoclasts formation (Li et al., 2005) and ecdysone type compounds stimulate proliferation of osteoblast-like UMR106 cells (Li et al., 2001).

Dioscorea spongiosa

Several reports demonstrated that glycosides, diarylheptanoids and lignans contained by the 90% ethanol fraction of water extract of the rhizomes of *Dioscorea spongiosa* (DS) not only significantly stimulate osteoblastic proliferation but also powerfully inhibit osteoclastic formation and bone resorbtion (Yin et

al., 2004b). Twenty-two glycosides were isolated from the 90% ethanol fraction of water extract of DS. While glycosides appear to stimulate osteoblastic proliferation and mineralization, diarylheptanoids and lignans are powerful inhibitors of osteoclastic formation and bone resorption, reporting a simultaneous weaker stimulatory activity of osteoblastic proliferation and mineralization (Yin et al., 2004a, b, 2010).

Carthamus tinctorius L

The Honghwain (HHI), *Carthamus tinctorius L*. seed extract, specific of the Korean herbal medicine and Herbimycin A are a novel class of Src-tyrosine kinase inhibitors that decrease cyclooxygenase-mRNA levels as well as prostaglandin E_2 production. Tyrosine kinase(s) seem to play a role in the signal transduction of cyclooxygenase -2 in mouse calvarial osteoblasts. HHI decreases dose-dependently the hypercalcemia induced in mice by IL-1β and partly acts against bone loss and micro-architectural changes in young OVX rats (Yuk et al., 2002). Another Korean herbal formulation, comprised of an herb of *C. tinctorius L*. seed and *Hominis Placenta*, which seems to inhibit IL-1ß-induced bone resorption is Honghwain-Jahage (Hong et al., 2002).

Cuscuta chinensis

To-Sa-Za (TSZ) is the dry seed of *Cuscuta chinensis Lam*. It is suggested that TSZ has osteogenic effects. Sustaining these, it was demonstrated that the aqueous extract of TSZ mildly promoted the proliferation of human osteoblast-like MG-63 cells and increased ALP, collagen and BMP-2 mRNA expression and mineralization of MG-63 cells (Yang et al., 2009). The clinical use of TSZ in the treatment of osteoporosis is further supported by a recent study, which demonstrates that kaempferol and hyperoside are the active compounds with an osteogenic effect in TSZ (Yang et al., 2011).

CONCLUSION

To conclude, the use of alternative therapies sourced from some medicinal plants and natural products in preventing and treating postmenopausal osteoporosis while avoiding significant risks associated with hormone replacements and other anti-fracture therapies, might be achieved. Overall, experimental studies are promising, showing the systematic, beneficial activities of *Epimedium's* metabolites and other Asian plants on bone metabolism. However, several questions need to be addressed; the optimal dosage and the mechanism of actions by which compounds from different plants have bone-protective effects are to be cleared, and the active constituents of these herbs as well as their pharmacological and toxicity profiles should be further investigated. Moreover, the pharmacological studies so far have mostly been performed with animals. Therefore, there is an utmost urge for prospective, randomized, clinical studies in humans to confirm this traditional phytotherapy.

Abbreviations:

AB, *Achyranthes bidentata*; **ALP**, alkaline phosphatase; **AP-1**, activator protein-1; **AS**, *Acanthopanax senticosus*; **ASA**, asperosaponin; **BMD**, bone mineral density; **BMP**, bone morphogenetic proteins; **DAW**, dipsacus asper Wall; **DS**, dioscorea spongiosa; **ER**, estrogen receptor; **ERK**, extracellular signal-regulated kinase; **FC**, fructus cnidii; **FLL**, fructus ligustri lucidi; **HRT**, hormone replacement therapy; **IGF-1**, insulin-like growth factor-1; **IL**, interleukin; **NF-κB**, nuclear factor-κappaB; **OC**, osteocalcin; **OPG**, osteoprotegerin; **OSX**, Osterix; **OVX**, ovariectomized; **RANKL**, receptor activator of NF-κB ligand; **SRB**, saikokaryukotsuboreito; **TCM**, traditional Chinese medicine; **TF**, total flavonoid; **TNF**, tumor necrosis factor; **HHI**, Honghwain; **TSZ**, To-Sa-Za.

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