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OSTEOPROTECTIVE MEDICINAL PLANTS - PART 1
(A HUMAN CLINICAL EVIDENCE-BASED REVIEW)

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Abstract

Background. Osteoporosis is a bone metabolic disease affecting a large percentage of aging population, which leads to an increased risk of fractures and has a negative impact on life quality. The available treatments for osteoporosis are effective, but are associated with several severe adverse reactions, hence the interest for alternative treatments devoid of such redoubtable side effects. Medicinal plants represent a viable resource for new therapeutic agents.
The purpose of this review is to provide an overview about the medicinal plants that have been reported to have anti-osteoporotic effects in human clinical studies.
Materials and Methods. Relevant studies found in PubMed database, pertaining to efficacy in humans, mechanism of action, osteoactive phytochemicals and safety, were selected. For the inquiry, keywords such as "medicinal plant", "osteoporosis", "bone", "fracture", "osteoclast" and "osteoblast" were used in various combinations. The information extracted was integrated with the traditional knowledge on the correspondent medicinal plants.
Results. Eight medicinal plants (*Cimicifuga racemosa, Cissus quadrangularis, Eleutherococcus senticosus, Epimedium spp., Glycine max, Pueraria spp., Panax notoginseng, Salvia milthiorriza*) were selected. Mechanisms involved include the activation of osteoblasts, inhibition of osteoclastogenesis, estrogen-like activity, anti-inflammatory activity, inhibition of collagen degradation by cathepsin K.
Conclusion. Several medicinal plants have been included in clinical studies successfully targeting osteoporosis, thus showing the potential to modulate bone resorption and bone formation.

Keywords: *Cissus quadrangularis, Cimicifuga racemosa, Eleutherococcus senticosus, Epimedium, Glycine max, Pueraria, Panax notoginseng, Salvia milthiorriza*, osteoporosis, fracture

List of abbreviations: BMD- bone mineral density; CQ- *Cissus quadrangularis;* CR- *Cimicifuga racemose;* ES- *Eleutherococcus senticosus*; IGF- insulin like growth factor; OPG- osteoprotegerin; OVX-M – ovariectomized mice; OVX-R- ovariectomized rats; PC – *Pueraria candollei;* PL – *Pueraria lobate;* PN- *Panax notoginseng;* RANK- receptor activator of NF-kB; RANKL- receptor activator of NF-kB ligand; ROS – reactive oxygen species; Runx 2- runt related transcription factor 2; SM- *Salvia milthiorriza*

Introduction

Osteoporosis and osteopenia (low bone density) are bone metabolic diseases affecting a large percentage of aging population, increasing the risk of fractures and having a negative impact on quality of life patients. Risk factors for osteoporosis are: hormonal related risk factors (menopausal and andropausal hormonal disturbances, early menopause,

hyperparathyroidism, hyperthyroidism), environmental related risk factors (e.g. dioxin-related compounds, heavy metals), nutrition-related risk factors (vitamin D, calcium deficiencies), lifestyle related risk factors (e.g. smoking, sedentarism), drugs (corticosteroids, anticonvulsants, aromatase inhibitors, gonadotropin-releasing hormone agonists), advanced age, female gender (Gonzalez-Macias et al., 2015; Paunescu et al., 2013; Rzymski et al., 2015).

Osteoporosis is caused by disturbances of bone remodeling process. The bone tissue is undergoing permanent build-up by osteoblasts and breakdown by osteoclasts. A good dynamic balance between the osteoblastogenesis and osteoclastogenesis is the key for a bone matrix of a high quality. The disbalance occurs especially when the breakdown process overwhelms the building process, being triggered by the risk factors (Leung and Siu, 2013).

There are several factors important for osteoblastogenesis, such as runt related transcription factor 2 (Runx 2) involved in osteoblast differentiation. Osteocalcin is a bone matrix protein produced by osteoblasts, which is involved in the regulation of bone mineralization.

Osteoblast and osteoclast activity is regulated by various factors, including growth factors (IGF, TGFβ, PDGF), bone morphogenetic proteins (BMP), hormones (parathormon, thyroid hormones, growth hormone, insulin, prolactin, sexual hormones, retinoids), vitamins (vitamin D3) (Hadjidakis and Androulakis, 2006).

Osteoclasts begin the process of resorption when osteoblasts are secreting RANKL, a pro-osteoclastogenic cytokine. RANKL interacts with receptor activator of NF-kB (RANK) activating the osteoclast differentiation, and leading eventually to the bone resorption (Leibbrandt and Penninger, 2008). Osteoprotegerin (OPG) is a protein secreted by osteoblasts, which opposes RANKL effects, by binding to it and inactivating it (Leung and Siu, 2013).

Biomarkers for bone turnover include bone resorption markers (pyridinoline, deoxypiridinoline, N-terminal and C-terminal telopeptides of type I collagen, hydroxyproline, tartrate-resistant acid phosphatase), and bone formation markers (osteocalcin, bone alkaline phosphatase, N-terminal and C-terminal propeptides of procollagen type I) (Eastell, 2016). Marrow adipogenesis is negatively correlated with bone strength and integrity (Fan et al., 2015).
The biomarkers are not useful for diagnosis, but only for monitoring the evolution of disease.

The available treatments for osteoporosis are effective, but are associated with several severe adverse reactions. Hormone replacement therapy has neoplastic (breast) and cardiovascular risks. Bisphosphonates enhance the rigidity of cortical bone, leading to increased risk of long bone fractures. Hence there is an increasing interest for alternative treatments devoid of such redoubtable side effects.

Several mechanisms have been suggested to be responsible for the medicinal plant effects on the bone remodeling cycle: activation of osteoblasts, modulation of osteoclastogenesis, inhibition of collagen degradation by cathepsin K, promotion of angiogenesis, inhibition of adipogenesis (Che et al., 2016; Guo et al., 2014; Yang et al., 2014).
The purpose of this review is to summarize the available scientific information obtained from medical databases and literature on medicinal plants that have been reported to have osteogenic activity in vitro, in animal models and also in human clinical studies.

Materials and Methods

A literature search was performed using the following phrase “medicinal plants OR herb AND osteoporosis”, “medicinal plants OR herb AND fracture”, “medicinal plants OR herb AND bone/osteoblast/osteoclast”, “specific herb latin name OR specific herb English name AND osteoporosis” (e.g. *Cimicifuga racemosa* OR black cohosh AND osteoporosis”), “specific herb latin name/herb English name AND fracture/bone/osteoblast/osteoclast” (e.g. *Cimicifuga racemosa* OR black cohosh AND fracture”) in PubMed database.

Selection criteria

Relevant studies found in PubMed database were collected pertaining to efficacy in humans (regardless of study design, language, year of publication or publication status), mechanism of action (in vitro study, animal study, human clinical study) and safety. Standardized criteria were utilized for selection. At least one human clinical study was inclusion criteria, while lack of human evidence was the exclusion criteria. Afterwards, the corresponding studies were analyzed. Information on the traditional use of these medicinal plants was also obtained by a manual search in various books on Traditional Chinese Medicine or Ayurveda.

Data Analysis

Data extraction and analysis were performed by professionals conducting medical research or clinical work at academic level. The most significant results for our topic were retrieved. Data were verified by a second author.
Eight medicinal plants belonging to six families were selected and presented in the alphabetical order of their latin name: 1 plant – Ranunculaceae (black cohosh), 1 plant – Vitaceae (harjor), 2 plants – Araliaceae (Siberian ginseng, notoginseng), 1 plant – Berberidaceae (horny goat weed), 2 plants – Leguminosae (soy, kudzu), 1 plant – Lamiaceae (red sage).

Osteoprotective medicinal plants
***Cimicifuga spp.*, fam. Ranunculaceae**

Traditional knowledge

The roots and rhizomes of black cohosh, *Cimicifuga racemosa* (CR), or *Actea racemosa*, have been used for centuries by native Americans as emmenagogue, galatogogue and anti-rheumatic in female ailments and joint disorders. The plant is traditionally prescribed as tincture, fluid extract, infusion or decoction (Khan and Abourashed, 2010).

In vitro studies

A CR ethanolic extract failed to promote osteoblast proliferation *in vitro* but stimulated bone nodule formation in association with increased expression of Runt-related transcription factor 2 (runx2) and osteocalcin genes, effects probably mediated by estrogen receptors (Chan et al., 2008).

Animal studies

Several studies endorsed the effectiveness of CR in protecting the bone from the estrogen scarcity of postmenopause. The administration of *C. heracleifolia* Komarov and *C. foetida* L *rhizoma* induced an increase in bone mineral density (BMD) in ovariectomized rats (OVX-R), the responsible active principles being some triterpenoids (Li et al., 1997).

CR preparations seem to contain selective estrogen receptor modulators (SERMs) as it exerts estrogen-like osteoprotective action of an intensity comparable to that of estrogens, especially on osteoblasts (Wuttke et al., 2003), preventing the decline of BMD and decreasing the serum osteocalcin level, but without influencing uterine weight or the expression of estradiol-regulated genes (Seidlova-Wuttke et al., 2003; Seidlová-Wuttke et al., 2003). CR lowered the urinary concentration of bone-loss markers pyridinoline and deoxypyridinoline and improves bone histology (Nisslein & Freudenstein, 2003).

On a model of OVX-R, CR was able to exert significant bone-sparing effect, as documented quantitatively by computer tomography (Seidlová-Wuttke et al., 2005).

The bone-protective effect of *Cimicifuga* triterpenoids was devoid of the undesired proliferative effects on the uterus exerted by the estrogens in ovariectomized mice (OVX-M) (Li et al., 2007).

CR extract given to OVX-R improved bone repair after fracture, inducing better trabecular network and endosteal healing, resulting in an quasi-physiological bone recovery (Kolios et al., 2010b). Nonetheless this effect seems to depend upon the severity of preexisting osteopenia, being wiped out in advanced cases (no improvement in the rate of the healing process), although a modest amelioration in the trabecular bone production (i.e. endosteal repair) and callus properties still can be noticed (Kolios et al., 2010a).

Given to OVX-M the rhizome of *C. heracleifolia* was beneficial for the trabecular bone (preventing the decline in mass, volume, trabecular number and thickness, and BMD, and preserving the structure model index), but not for the cortical bone. No proliferative adverse effect on the uterus was noted (Ahn et al., 2012).

The triterpene fraction of CR extract administered to OVX-R partially prevented the deterioration of trabecular bone mineral status and microarchitecture and the expansion of the bone marrow fat, which is known as a source of pro-inflammatory cytokines able to activate osteoclasts and to silence osteoblasts (Seidlova-Wuttke et al., 2012).

An isopropanolic extract of CR experimented on OVX-R proved bone-preserving activity (BMD, trabecular architecture, mechanical stiffness) comparable to that of estradiol, if it is administered long enough (at least 3 months) (Cui et al., 2013).

Human clinical studies

A double-blind, placebo-controlled trial on postmenopausal women pointed out the osteoblast stimulating activity of CR, mirrored by improved markers of bone turnover (Wuttke et al., 2006). Other researchers demonstrated reduced bone resorption (a drop in the urinary level of N-telopeptides) and increased bone formation (higher concentration of alkaline phosphatase) in postmenopausal women who were given a CR extract, but failed to demonstrate a direct stimulating effect of the serum from treated women on a culture of osteoblasts (García-Pérez et al., 2009). However, other researchers failed to demonstrate a bone-favorable effect of CR extract in exercising early postmenopausal women (Bebenek et al., 2010). A significant shortcoming of this study was the absence of a CR-taking non-exercising comparison group, as the possibly positive effect of CR might have been lost in the well-known considerable favorable effect of exercise on BMD.

Active phytochemicals

A cycloartane triterpenoid glycoside isolated from CR, 25-acetylcimigenol xylopyranoside, blocked the NF-κB and extracellular signal–regulated kinase (ERK) pathways and hence strongly inhibits both receptor activator of NF-kB ligand (RANKL)- and TNFα- induced osteoclastogenesis (Qiu et al., 2007). Three other cycloartane-type triterpenoids from CR rhizome (xylosides of cimicidol, cimicidanol, and acetylacteol) have been shown (on cell cultures) to act synergically in hindering bone resorption by blocking both the genesis and the function of osteoclasts (Li et al., 2007).

Applied on osteoblastic cells, deoxyactein (isolated from CR) promoted cell growth and alkaline phosphatase activity, along with increased collagen content and mineralization, lowered the generation of reactive oxygen species (ROS) and of inflammatory mediators (including TNF-α, IL-6 and RANKL) known to promote osteoclast differentiation (Choi, 2013).

Actein, another triterpenoid from CR, is able to protect osteoblasts (specifically their mitochondria) against oxidative stress, beside reducing the generation of TNF-α and enhancing osteoblast function, osteocalcin and collagen production, alkaline phosphatase activity, and bone mineralization (Lee and Choi, 2014).

Safety

CR is generally considered as a safe herbal therapy if taken for a limited period, but further studies are needed to evaluate the safety over longer periods of time (Huntley, 2004). Several cases of acute liver injury, following consumption of CR were reported (Mahady et al., 2008). The mechanism suggested by the scientists was troxis necrosis of hepatocytes, which were gradually consumed and removed by lymphocytes (Enbom et al., 2014). A rigorous analysis of these cases showed only possible causality, and not probable or certain causality (Mahady et al., 2008; Teschke and Schwarzenboeck, 2009). Also, a meta-analysis of randomized controlled clinical trials for isopropanolic CR extract on 1020 women found no evidence of CR hepatotoxicity (Naser et al., 2011). Isolated cases of reversible complete heart block (McKenzie and Rahman, 2010), muscle damage were also reported (Minciullo et al., 2006), but only temporal relationship and the absence of other identified causal factors were invoked to support these claims.

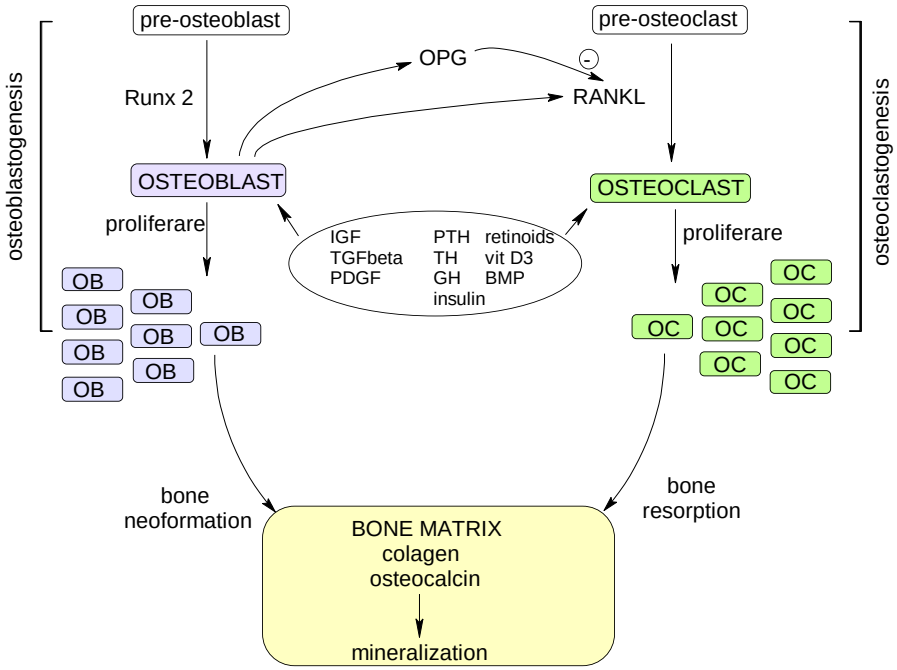

Figure 1: Main regulators of bone remodeling cycle (Legend: BMP- bone morphogenetic proteins, GH- growth hormone, OPG-osteoprotegerin , PTH- parathormon, RANKL-receptor activator of NF-kB ligand, Runx 2- runt related transcription factor 2, TH- thyroid hormones**)**

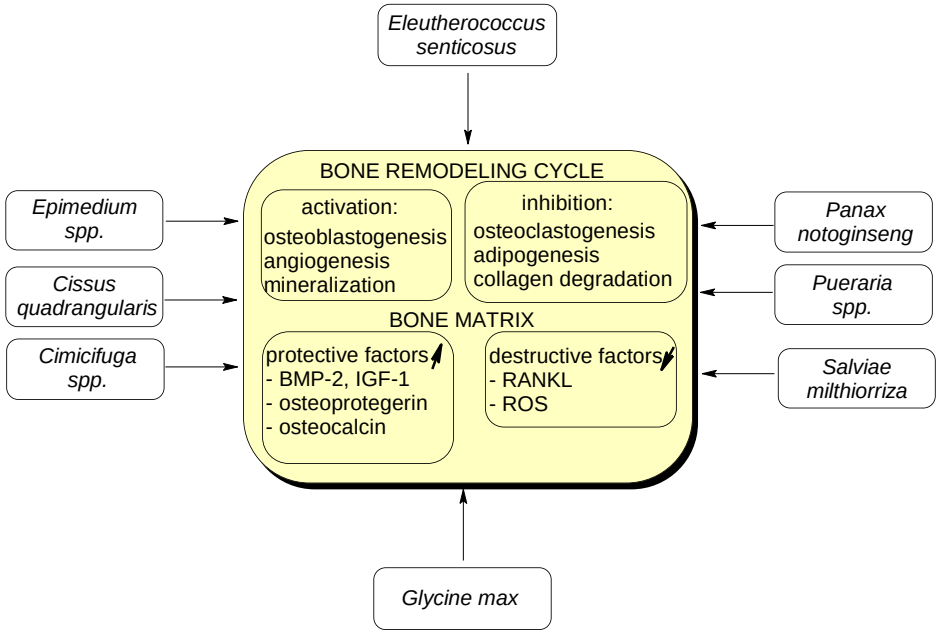

Figure 2: Medicinal plants with anti-osteoporosis and fracture healing activities proved in human clinical studies (Legend: BMP-2, bone morphogenetic protein 2; IGF-1, insulin like growth factor 1; RANKL- receptor activator of NF-kappaB ligand; ROS- reactive oxygen species)

***Cissus quadrangularis*, fam. Vitaceae**
Traditional knowledge

Cissus quadrangularis (CQ), commonly known as *harjor* in Hindi or *asthisamharaka* in Sanskrit (engl. bone seizer), is an Indian medicinal plant, used in Ayurveda to accelerate healing process of fractured bone and to treat swelling (Singh and Gilca, 2010). Stem (powder, decoction) or plant juice administered internally have been cited in Ayurveda for bone ligation properties. Stems are also used externally as paste or medicinal oil in fractures, dislocations or traumatic inflammation (Pandey, 2005).

***In vitro* studies**

CQ exhibited anabolic and osteogenic properties in several *in vitro* studies. It increased the mRNA expression of growth factors (IGF-I, IGF-II, IGF-IR), and Runx2, a key transcription factor involved in matrix mineralisation, in human osteoblast like SaOS-2 cells (Muthusami et al., 2011a, 2011b). A recent study showed that the ethanol extract of CQ enhanced osteoblast differentiation and mineralization of extracellular matrix (Tasadduq et al., 2017).

Animal studies

CQ extract was effective against diabetes-induced delayed fetal skeletal ossification, restoring the ossification centers in the neonatal pups of diabetic rats (Sirasanagandla et al., 2014). Several studies showed the capacity of CQ to reduce bone loss, as evidenced by the bone weight gain, density, strength, and calcium content in ovariectomised or orchidectomized animals (Jadhav et al., 2016; Potu et al., 2009). Maternal administration of CQ extract during pregnancy stimulated the development of fetal bone growth during the intra-uterine period in rats (Potu et al., 2008).

Human clinical studies

CQ as monotherapy, or in combination with *Moringa oleifera*, helped in reducing pain, swelling, tenderness, and fracture mobility, and accelerated the healing of maxillofacial fracture (Brahmkshatriya et al., 2015; Singh et al., 2011).

Active phytochemicals

Several phytocompounds, such as glycerolipids and squalene, showed the capacity to stimulate alkaline phosphatase and, moreover, displayed the synergistic effect of bone formation (Pathomwichaiwat et al., 2015). Ketosteroid content, which is currently used for the standardization of CQ supplements in USA, was not correlated with the plant effect on the bone parameters (mean bone density, strength, and calcium content) in an animal model of osteoporosis (Jadhav et al., 2016).

Safety

A systematic review on the randomized controlled trials available in the present concluded that no serious adverse effects were reported with the use of *Cissus quadrangularis* (Sawangjit et al., 2017).

***Eleutherococcus senticosus*, fam. Araliaceae**
Traditional knowledge

Eleutherococcus senticosus (ES), also known as Siberian ginseng, has been traditionally used to strengthen muscle and bone, in Northeastern Asia, e.g. Korea. Bark of stem or root, whole root and rhizome, as tincture, tea, powder, liquid, and solid extracts are traditionally used (Khan and Abourashed, 2010).

Animal studies

ES extract increased the femur BMD, and decreased serum levels of bone markers (e.g. alkaline phosphatase) , without affecting the uterus weight, and serum estradiol level in OVX-R(Lim et al., 2013). A herbal formula HT042, consisting of ES, *Phlomis umbrosa*, and *Astragalus membranaceus*, which is used in traditional Korean medicine to stimulate growth of children with short stature, induced longitudinal bone growth in adolescent or adult female rats (Kim et al., 2012, 2010). HT042 has also increased the expression of insulin-like growth factor-1, insulin-like growth factor binding protein-3, and bone morphogenetic protein-2 in the growth plate.

Human clinical studies

ES extract produced an increase in serum osteocalcin levels, but no changes in BMD in Korean postmenopausal women (Hwang et al., 2009).

Active phytochemicals

It is not clear yet, which phytochemicals from ES are responsible for the antiosteoporotic effect of the plant. One study showed that ciwujianoside-B, a minor saponin also found in ES, is able to increase the proliferation abilities of bone marrow cells and to provide radioprotection on the hematopoietic system in mice (Li et al., 2011).

Safety

ES is considered generally safe (Khan and Abourashed, 2010). Although, pharmacists advised caution in hypertensive patients because it has been documented to cause increase in blood pressure, tachycardia, and palpitations (Rasmussen et al., 2012). Elevated serum digoxin levels were reported in a patient taking digoxin and Siberian ginseng (McRae, 1996), but the case was debatable, the critics suggesting a possible botanical misidentification by clinical investigators (Awang, 1996). A more recent study showed that ES may cause either falsely increased or decreased values of serum digoxin due to interferences with the digoxin immunoassays (Dasgupta et al., 2003).

***Epimedium spp*, fam. Berberidaceae**
Traditional knowledge

Epimedium herbs, also known as horny goat weed, are species used as liver and kidney tonic in Traditional Chinese Medicine. It is indicated also in the treatment of bone diseases. Aerial parts (leaves, stems and petioles) are traditionally used as decoction, but not for a long term, since they could harm the yin and cause dizziness, dry mouth, thirst, nausea, nosebleeds (Hempen and Fischer, 2009).

In vitro studies

E. brevicornum extracts stimulated the proliferation of osteoblast-like UMR106 cells in vitro (Meng et al., 2005). *Animal studies. E. sagittatum* extract produced a significant reduction in the bone defect area on X-ray images and bone neoformation in rats with critical calvarias defects (Burim et al., 2016).

Human clinical studies

Recent clinical studies have suggested that *Epimedium* spp. have the potential, as monotherapy or in combination with other phytoingredients, to prevent or delay the onset of osteoporosis, and to decrease the risk of hip fractures (Indran et al., 2016). A recent controlled clinical trial of 24-month duration showed that a daily dose of *E. brevicorum* -derived phytoestrogen flavonoids (60 mg icariin, 15 mg daidzein, and 3 mg genistein) can prevent bone loss in late postmenopausal women, as shown by preservation of BMD at lumbar spine at 12 months, but not at the femoral neck (which is less metabolically active) until 24 months. It also decreased urinary levels of deoxypyrdinoline, a bone resorption biochemical marker (Zhang et al., 2007). This effect was not associated with a significant change in endometrial thickness and serum estradiol, therefore no risk of uterine hyperplasia.

Active phytochemicals

Epimedium prenylflavonoid derivatives have been reported to target several bone morphogenesis pathways in various cell lineages (e.g. mesenchymal stem cell, osteoblast, osteoclast) (Indran et al., 2016). Icariin, one of the mentioned compounds, has been proved to have multitarget antiosteoporotic activity, with simultaneous promotion of osteoblastogenesis, inhibition of adipogenesis, and prevention of osteoclast differentiation, in animal studies (Xue et al., 2016). Besides icariin, flavonoid fraction of *Epimedium* is also osteo-active, improving trabecular BMD and restoring the bone microarchitecture in OVX-R (Zhao et al., 2016). A study of systems pharmacology predicted that *Epimedium* phytochemicals may exert its benefits on bone health by direct regulation of several osteoporosis related targets, via estrogen like mechanisms (Xu et al., 2016).

Safety

It is safe when taken for periods not excessively long (Khan and Abourashed, 2010), and when used orally at common dosages of 5 g daily, or 300 ml of extract for six months (Ulbricht, 2016). It may become unsafe in patients with estrogen-sensitive conditions, cardiovascular disease, bipolar disorder, bleeding events, hypothyroidism, anticoagulant or antiplatelet treatment (Ulbricht, 2016).

***Glycine max*, fam. Leguminosae**
Traditional knowledge

Glycine max, also known as soybeans, are a traditional staple food in countries such as Korea, where *meju* and *doenjang* are two traditional fermented soybean preparations (Jeong et al., 2016).

Animal studies

Soy protein retards the onset of age-related bone loss (Blum et al., 2003; Kalu et al., 1988). Studies on OVX-R showed that the bone-protective action of a soy-rich diet is due to isoflavones (Arjmandi et al., 1998), daidzin, genistin, and glycitin among others (Uesugi et al., 2001). Several other studies corroborated the bone-sparing effect of soy isoflavone on OVX-R (Kim and Lee, 2005; Watkins et al., 2005; Wu et al., 2004) or their ability to positively influence the markers of bone catabolism (Mori et al., 2004) or the bone microarchitecture (Devareddy et al., 2006) and quality (better histomorphometric parameters, higher concentration of glycosaminoglycans and mature type I collagen fibers) (Santos et al., 2014), or to downregulate osteoclastogenesis (as indicated by the alterations in serum interleukin-6 levels) (Gallo et al., 2005). Soy isoflavones in combination with cello-oligosaccharides are useful in preventing bone disease in estrogen-lacking OVX-M (Fujii et al., 2016), while together with milk basic protein they seem to act synergically in maintaining bone health (Matsumoto et al., 2016). Sex hormone deprived male rats may also benefit from the bone-beneficial effect of soy isoflavones, albeit a modest one (Khalil et al., 2005). Soy isoflavones may be useful even during neonatal life: an early exposure increases bone strength, along with mineral density and trabecular inter-connectivity, later in life (Ward et al., 2016).

Human clinical studies

Soy isoflavones are useful for postmenopausal women in preventing bone loss (Chen et al., 2003; Huang et al., 2006) and in decreasing fracture risk (Zhang et al., 2005) or at least in favorably influencing the bone metabolism markers (diminished urinary levels of deoxypyridinoline) (Roudsari et al., 2005). The enhanced bone density may be related to the reduced level of inflammatory cytokines IL-6 and TNF-α (Chi and Zhang, 2013). A double-blind randomized parallel study on 200 menopausal women given soy isoflavones demonstrated reduced bone-resorption markers {such as type I collagen crosslinked beta C-telopeptide (βCTX)}, explained by the selective modulation of estrogen receptors (Sathyapalan et al., 2016), an ability arising probably from the geometrical similitude of the isoflavone molecule to that of 17-β-estradiol (Kaczmarczyk-Sedlak et al., 2013).

The bone-sparing effect of soy-protein products in postmenopausal women is sizeable only when the concentration of isoflavones is high (2.25 mg isoflavones/g protein) (Erdman et al., 2000; Potter et al., 1998). This effect extends to perimenopausal women (Alekel et al., 2000; Greendale et al., 2002) and to premenopausal women past the 30 years threshold of peak bone density (Greendale et al., 2002; Ho et al., 2001). This is not valid for younger women (Anderson et al., 2002), which is no surprise as no estrogen deficiency is expected in this latter age group. The effect in post-menopausal women is correlated with higher levels of IGF-I and is greater in those not on hormone replacement therapy (Arjmandi et al., 2003). The bone-reinforcing effect of isoflavones may be synergically assisted by progressive resistance exercises (Shenoy et al., 2013).

In postmenopausal women a diet abundant in soy protein is associated with increased BMD and decreased bone (Ho et al., 2003; Horiuchi et al., 2000; Somekawa et al., 2001). Nevertheless the influence is rather modest and longer treatments (more than 6 months) may be necessary for a sizeable effect to occur (Hsu et al., 2001). A small randomized, crossover, blinded study on 11 postmenopausal women was able to detect a slight (but significant) positive action of isoflavones from soy (but not from kudzu or red clover): a 9% reduction in bone resorption was noticed over a 50-day treatment period compared to 22% and 24% obtained with risedronate and estrogen plus progesterone respectively (Weaver et al., 2009).

The bone mineral content of infants fed soy formula appears to be similar to those fed human milk (Bainbridge et al., 1988) (Hillman, 1988; Mimouni et al., 1993).

However some studies *did not* sustain the hypothesis of a positive effect of isoflavones-rich diet on bone turnover in pre- and postmenopausal women (Wangen et al., 2000), in postmenopausal women (Gallagher et al., 2004; Kreijkamp-Kaspers et al., 2004; Nagata et al., 2002; Roughead et al., 2005), in postmenopausal monkeys (Register et al., 2003), in premenopausal rats (Nakai et al., 2005) or found no correlation with the bone resorption indices, suggesting that isoflavones-containing soy protein are devoid of bone-protective estrogenic effects (Dalais et al., 2003) or found a positive influence on bone formation markers but not on actual bone health (Arjmandi et al., 2005).

This apparent contradiction may arise from the necessity of high doses, long periods of intake and/or early onset of the diet for a palpable effect to occur. Soy isoflavones may be significantly beneficial only when administered early (immediately after menopause or even in the perimenopausal period) (Reinwald and Weaver, 2006).

Safety

There are certain concerns regarding side effects and safety of soy isoflavones, in case of an uncontrolled consumption, due to their weak estrogenic activity (Diel et al., 2017; Lehmann et al., 2017). Although, European Food Safety Authority (EFSA) stated that "there are no available data supporting the potential adverse effects of isolated isoflavones on the human mammary gland, uterus or thyroid in healthy postmenopausal women" (Lehmann et al., 2017). Another aspect related to soybean consumption, is that soybean is the first and single genetically modified food lawfully recognised as allergenic (Selb et al., 2017). Nonetheless, in terms of bone benefits and safety, we should dissociate soybean consumption from soy isoflavones supplementation, since soy isoflavone content is reduced by food preparation procedures typical to Asian cuisine (but not to modern cooking practices) (Fernandez-Lopez et al., 2016). In conclusion, it seems that additional human clinical studies are required to define more precisely the safety level of soy isoflavone intake.

***Panax notoginseng*, fam. Araliaceae**
Traditional knowledge

Panax notoginseng (PN), known as *sanqi* in Chinese, is traditionally used to remove blood stasis, to stop hemorrhage, and to diminish pain. Therefore it is indicated for traumatic injuries associated with bleeding, swelling and aching (Zhanwen and Liang, 2009). Roots of the plant are used as decoction or powder (Hempen and Fischer, 2009).

In vitro studies

PN extract inhibited osteoclastogenesis by suppressing MAPK in LPS-activated RAW264.7 cells, showing therapeutic potential in periodontal diseases associated with bone loss (Jang et al., 2011).

Human clinical studies

One recent clinical study confirmed the traditional claim concerning the benefits of PN in traumatic injuries: association of PN to conventional treatment was significantly more efficient than conventional treatment alone, in terms of clinical symptoms, in patients with multiple fractured ribs and pulmonary contusions caused by the 2008 Wenchuan earthquake (Tianhong et al., 2014). It accelerated the recovery and decreased the systemic analgesics administration.

Active phytochemicals

Saponins are considered to be the main osteo-active phytochemicals from PN. PN saponins prevented bone loss and microarchitecture alteration by simultaneous stimulation of bone neoformation via osteoblast activation, and inhibition of bone resorption via suppression of osteoclast turnover in OVX-R (Fan et al., 2015). They also decreased marrow adipogenesis. Other effects induced by PN saponins [!!merge şi fără, zic eu]: stimulation of collagen synthesis and mineralization in osteoblasts (Ji et al., 2015), activation of angiogenesis in rat bone marrow mesenchymal stem cells (Zheng et al., 2013), promotion of proliferation and osteogenic differentiation of bone marrow stem cells, inhibition of bone resorbtion through reduction of RANKL/OPG expression via Wnt/-catenin signaling pathways *in vitro* (Chen et al., 2012) .

Safety

Oral administration of PN powder produced no cardiac, hepatic, renal, splenic or gastrointestinal signs of toxicity in animal studies (Khan and Abourashed, 2010). Side effects of injectable PN saponin use in humans are rare, skin rash, pustules, fever and elevated circulating neutrophil counts being reported in a few cases (Khan and Abourashed, 2010; Wang et al., 2016; Yin et al., 2014). Over-dosage of PN saponin may cause nausea, vomiting and nose bleeding (Wang et al., 2016).

***Pueraria spp.*, fam. Leguminosae**
Pueraria lobata

Traditional knowledge

Pueraria lobata (PL) or *kudzu* in Chinese, is a traditional herbal remedy commonly used for treatment of cold, flu, fever without sweating, diarrhea, pathological thirst, exanthemas (Hempen and Fischer, 2009; Khan and Abourashed, 2010) but also indicated for menopause-associated diseases, including osteoporosis (Woo et al., 2003). The part used is mainly the root, but also flowers are sometimes administered (e.g. for hangover). PL is considered an ethnic food, the root cut into slices being used in soups, while the starch (flour) is employed in pastries and as a thickener (Khan and Abourashed, 2010).

Animal studies

PC root as monotherapy or in combination with other herbs (e.g. *Rehmannia glutinosa*) or methods (e.g. exercise) showed the capacity to preserve bone mass in various animal models of osteoporosis (e.g. OVX-R fed a high-fat diet), via decreased number of osteoclasts, without producing uterine hypertrophy (Ok et al., 2015; Tanaka et al., 2011).

Pueraria Candollei var. Mirifica
Traditional knowledge

Pueraria Candollei (PC) *var. Mirifica* , also known as *white kwao krua*, is used as rejuvenative in many tropical countries (Wiriyakarun et al., 2013). PC is highly estrogenic and has evidence-based regenerative effect on bones.
In vitro studies. PC extract increased the proliferation, expression of alkaline phosphatase and type I collagen in primary baboon osteoblasts (Tiyasatkulkovit et al., 2014).

Animal studies

Beneficial effects of PC on bone have been validated in non-human primates, which are more closely related to humans than rodents. PC alleviates cortical bone loss in naturally menopausal monkeys (Kittivanichhkul et al., 2016).

Human clinical studies

PC treatment for 24 weeks induced a significant decrease in bone-specific alkaline phosphatase levels in healthy postmenopausal women aged 45 to 60 years old (Manonai et al., 2008).

Active phytochemicals

The scientific basis for the bone mass modulator activity of *Pueraria* spp. may be their high content of phytoestrogens, like isoflavones, etc. Puerarin, the major isoflavone glycoside in *Pueraria* spp., reversed the negative effects that low protein maternal diet had on the microenvironment of the fetal bone, improving the bone biomarkers (e.g. insulin-like growth factor-1, bone-specific alkaline phosphatase, osteocalcin, osteoprotegerin, RANKL) in the serum of rats with intrauterine growth restriction (Chen et al., 2016). This compound may promote the expression of estrogen receptors (ERα, ERβ) and steroid hormone receptor coactivator (SRC)-1(Wang et al., 2014), and oppose cisplatin-induced apoptosis in human osteoblasts (Wang et al., 2013). Nevertheless, puerarin may also exert its anti-osteoporotic action, also, through an alternative pathway which is independent of estrogen receptor (Michihara et al., 2012). Supplementation with puerarin in combination with other phytoestrogens (3 capsules daily, each capsule contained 143 mg puerarin and 168 mg phytoestrogenic aglycon in total) failed to showed improvement in bone resorption in one human clinical study (Weaver et al., 2009).

Safety

PL is safe when used appropriately (Khan and Abourashed, 2010). Certain minor side effects of PL were reported in a few human studies: increased triglyceride levels, gastrointestinal distress (e.g. nausea, dyspepsia, vomiting, and bloating), anxiety (Ulbricht et al., 2015).

***Salviae miltiorrhiza*, fam. Lamiaceae**
Traditional knowledge

The root and rhizome of *Salvia miltiorrhiza* (SM), also known as red sage in English or *danshen* in Chinese, has been used to treat skeletal diseases in traditional Chinese medicine (TCM), by removing liver and blood stasis (Guo et al., 2014; Zhanwen and Liang, 2009). SM is considered one of the best remedy for activating blood circulation. It is traditionally used as decoction, effective in the treatment of cardiac ischemia, irregular menses, dysmenorrhea, amenorrhea, abdominal masses, and insomnia associated with cardiac symptoms, such as palpitations (Hempen and Fischer, 2009).

In vitro studies

SM enhanced bone remodeling by regulating the gene expression of alkaline phosphatase, osteocalcin, osteoprotegerin, and RANKL) on osteoblastic cells MC3T3-E1 *in vitro* (Chin et al., 2011).

Animal studies

SM improved the BMD in diabetic rats in early stage, showing an inhibitory effect on alveolar bone osteoporosis (Miao et al., 2012), and prevented the occurrence of hyperlipemia- induced osteoporosis in mice (Zhang et al., 2008).

Human clinical studies

Guo et al identified 36 clinical trials which used SM as monotherapy or in combination with other medicinal plants or ingredients to treat osteoporosis, with high efficacy and no toxicity, although some of the studies showed certain design limitations (Guo et al., 2014). SM injection and implantantion of calcium phosphate cement/SM drug delivery system by minimal invasive surgery improved the microcirculation and reconstruction of the bone, in human subjects with ischemic or avascular necrosis of femoral head, as evaluated by digital substruction arterography and X-ray films (Huang et al., 2008; Jiang et al., 2009; Wang et al., 2007).

Active phytochemicals

Several active components isolated from the root of SM, have been reported to have various benefits for bone health. Salvianolic acid B, a phenolic acid, accelerated the bone healing in a rat tibia fracture model, by increasing activity of alkaline phosphatase (He and Shen, 2014), and prevented bone loss in prednisone-treated rats through stimulation of osteogenesis and bone marrow angiogenesis (Cui et al., 2012). Dihydrotanshinone and cryptotanshinone showed inhibitory activities against the collagenase activity of the osteoclast-resident cathepsin K (Guo et al., 2014).

Safety

SM overdosage may rarely cause minor side effects (e.g. dry mouth, dizziness, lassitude, numbness, etc) that usually disappear without interrupting plant administration (Wang, 2010). SM should not be associated with warfarin, because it could amplify the anticoagulant effect (Wang, 2010). According to TCM, SM use in pregnant women or in subjects with bleeding tendency is forbidden (Hempen and Fischer, 2009; Wang, 2010). Animal studies showed only low toxicity (Khan and Abourashed, 2010).

Conclusion

Overviewing the medical literature on medicinal plants used for promoting osteogenesis, we found a scarcity of human clinical studies in this field. Although medical scientists have found that many herbs and phytochemicals have antiosteoporotic affect *in vitro* or animal studies, their effects on bone metabolism and homeostasis in human subjects are still not sufficiently studied.

Nevertheless, the eight medicinal plants selected (*Cissus quadrangularis, Cimicifuga racemosa, Eleutherococcus senticosus, Epimedium spp., Glycine max, Pueraria spp., Panax notoginseng, Salvia milthiorriza*) showed efficacy in preventing osteoporosis or accelerating fracture healing.

The herbal activity of these plants was mediated through various mechanisms: modulation of various key signaling pathways involved in osteoblastogenesis, osteoclastogenesis, bone marrow angiogenesis, estrogen-like activity, antioxidant and anti-inflammatory properties.

Recent major efforts were done in the field of osteoporosis treatment, in order to develop newer agents, although not all of them were successful. Odanacatib (an oral inhibitor of cathepsin K for post-menopausal women with osteoporosis), after a successful progression through Phases II clinical trials, was abandoned during the Phase III of clinical trials, due to its high risk of stroke (Mullard, 2016). Interestingly, certain herb extracts or phytochemicals showed also the potential to inhibit cathepsin K (e.g. dihydrotanshinone and cryptotanshinone from *Salviae miltiorrhiza*) (Cui, 2014; Guo et al., 2014), at the same time being devoid of severe side effects, such as those encountered with the synthetic cathepsin K inhibitors.

Further human clinical studies are required to confirm herbal osteoprotective activity, to standardize the therapeutic dosage and to evaluate safety. We estimate that broader investigation of the herbal derived medicines might reveal not only new bone-friendly phytochemicals, but also new perspectives on the therapeutic approaches in osteoporosis.

Conflict of Interest: Authors declare that is are no conflict of interest

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