

• Reviews •

Prevention and Treatment of Osteoporosis with Chinese Herbal Medicines

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Abstract: In this paper, laboratory reports, medication rules, formulating principles, and research methods are summarized and analyzed, including single herb, compound herbs, and the problems in the prevention and treatment of osteoporosis (OP) within the past decade. With widely recognized efficacy, satisfying achievements have been achieved in preventing and treating OP with Chinese herbal medicines (CHM). However, due to the complex constituents, the pharmacological activities and mechanism of CHM are not clear yet, and there is no unified standard on the diagnosis and syndrome differentiation of OP and the efficacy evaluation of CHM in the treatment. Accordingly, the research in the future should focus on the pharmacology and standardization of CHM in treating OP.

Key words: Chinese herbal medicines; efficacy evaluation; osteoporosis; pharmacological activities; prevention and treatment

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Introduction

Osteoporosis (OP) is a metabolic bone disease that leads to an increasing risk of fracture. In OP, micro-architecture of bone is damaged, and the proportions of bone minerals and bone matrixes are reduced. Clinically, OP falls into three categories, primary OP, secondary OP, and idiopathic OP (Table 1).

The formation of bone tissue in the body is a continuous process of turnover, including bone remodeling and destructing. The process of bone remodeling is controlled by a balance of bone formation and bone

resorption (Roodman, 1996). Excessive bone resorption results in bone abnormalities such as OP, which is characterized by a reduction in bone mass and a higher incidence of bone fractures (Weinreb, Rodan, and Thompson, 1989). Currently, the treatment of OP is mainly focused on using Western medicines, which could be divided into two parts, bone resorption inhibitors and bone formation stimulants. However, these drugs do not address the multifactor caused OP. In particular, they do not mitigate the detrimental effect on bone marrow fat metabolism and circulatory system

Table 1 Brief description of three categories of OP

Categories	Types	Syndromes
postmenopausal OP	Type I	often happens in women after menopause
senile OP	Type II	occurs as a result of calcium deficiency and occurs in individuals over 70 years old
	Type III	triggered by diseases or drugs, including endocrine OP, nutritional deficiencies OP, drug-induced OP, renal OP, and so on
idiopathic OP	Type IV	more common in 8—14 year-old teenagers or adults, mostly with a genetic family history, more women than men

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(Kerachian, Seguin, and Harvey, 2009; Weinstein, 2010). For the drawbacks of Western medicines, we should seek effective ways from other treatments, such as Chinese herbal medicines (CHM).

Traditional Chinese medicine theory on OP

CHM have been used for more than 2000 years as a common treatment. According to traditional Chinese medicines (TCM) theory, kidney stores essence, governs bone, and produces marrow, and deficiency of kidney is most closely related to OP. On account of its clinical symptoms (lumbago, fracture-prone, and humpback), OP could be classified as “Guwei” or “Gubi”. From the perspective of TCM, kidney is the innate origin of human body and the waxing and waning of kidney Qi directly affect the growth, development, and aging of human body. Marrow is stored in the bone and nourishes the bone. Sufficient kidney essence could make the bones strong. For OP patients, the deficiency syndrome is mainly the result of kidney deficiency, while the excess syndrome points to blood stasis and Qi stagnation. On the other hand, OP is related to not only the kidney but also the spleen. These two organs are dependent on each other, and they have a mutually reinforcing relationship in physiology while they have a mutually destructive relationship in pathology. In general, kidney deficiency is the primary cause of OP, and spleen deficiency is its secondary factor.

In recent years, CHM have achieved many effects on the prevention and treatment of OP (Zhang and Li, 2012; Yue *et al.*, 2009). From the perspective of its chemical ingredients and action mechanism as well as categories of OP, the present review would elaborate single herbs and compound herbs applied in the treatment of OP.

Single herbs

Epimedii Folium (Yinyanghuo) *Epimedii Folium* is the dried leaves of *Epimedium brevicornum* Maxim., *E. sagittatum* (Sieb. et Zucc.) Maxim., *E. pubescens* Maxim., or *E. koreanum* Nakai (Berberidaceae). The polysaccharides and total flavonoids are the main components of *Epimedii Folium* (Meng *et al.*, 2009). Pharmacokinetic experiments showed that icariin (Fig. 1) could dose-dependently promote osteogenic differentiation of rats' bone marrow stromal cells (rBMSCs) at each stage of culture by the increasing of

alkaline phosphatase (ALP) activity and the colony forming unit-fibroblast (CFU-F) stained positive number for ALP at early stage as well as by the enhancement of osteocalcin secretion and the deposition of calcium level at late stage. The most effective concentration of icariin is 10 $\mu\text{mol/L}$ (Ma, 2007). Icariside II (Fig. 1), which is the main metabolite of icariin after it is given, has more powerful effects on bone formation. It also improves the osteogenic differentiation of rBMSCs, which is the same with icariin in other effects. Additionally, icariside II also enhances the gene expression of basic fibroblast growth factor, insulin-like growth factor-1 (IGF-1), Osterix, and Runx-2.

Salviae Miltiorrhizae Radix et Rhizoma (Danshen) *Salviae Miltiorrhizae Radix et Rhizoma* is the dried roots and rhizomes of *Salvia miltiorrhiza* Bge. (Labiatae). Salvianolic acid B (Sal B) and tanshinone II_A (Tan II_A) (Fig. 1) are the bioactive ingredients in Danshen. Clinical experiments demonstrated that Tan II_A could efficiently reduce biological indexes of bone resorption, lower bone turnover, and prolong or block bone loss in postmenopausal women with OP (Wang, Zhang, and Yang, 2006). Recent studies showed the

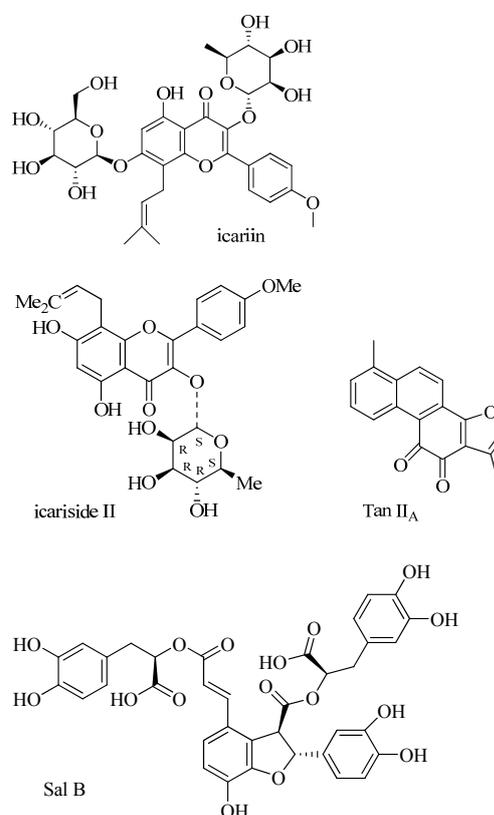


Fig. 1 Structures of icariin, icariside II, Tan II_A, and Sal B

following facts: (1) *In vivo* study: Daily treatment with Sal B in glucocorticoid (GC)-induced male rats could prevent cancellous bone loss and adipogenesis increasing, while it could increase cancellous bone formation rate and improve local microcirculation by capillary dilation; (2) *In vitro* study: Sal B stimulated the differentiation of osteoblast (OB) from rBMSCs, increased OB activities, decreased GC-associated adipogenic differentiation by down-regulation of the peroxisome proliferator-activated receptor α mRNA expression, and increased Runx-2 mRNA expression without OB inducement (Cui *et al.*, 2012).

***Rehmanniae Radix Praeparata* (Shudihuang)**
Rehmanniae Radix Praeparata is the processing products of root tubers of *Rehmannia glutinosa* Libosch. (Scrophulariaceae). Shudi has been widely used as a herbal medicine in Eastern Asia for more than 2000 years. The major constituents of the herb are β -sitosterol and mannitol. Recently, Kim *et al.* (1999) demonstrated that Shudi inhibited the secretion of both interleukin-1 (IL-1) and tumor necrosis factor- α (TNF- α)

from mouse astrocytes. Stashenko *et al.* (1987) reported that TNF- α could synergize with IL-1 in their ability to decrease bone resorption. The significant effects of Shudi extracts on OB were shown as following: (1) to increase both the proliferation of OB and ALP activity; (2) to increase the expression of bone-related genes; and (3) to increase osteoprotegerin secretion markedly. The effects on the osteoclast (OC) were shown as below: (1) to decrease the resorption areas; (2) to alleviate the decreasing in the trabecular bone marrow depression (BMD); and (3) to increase the cortical bone thickness and trabeculation of the bone marrow spaces *in vivo* (Oh *et al.*, 2003). The introductions of other ten single herbs were shown in Table 2.

Except for all the single herbs mentioned above, more than 80 single herbs with efficacy in treating OP have also been reported. These drugs could reinforce kidney Qi or enrich blood, respectively. Their efficacies in treating OP exhibited in four aspects: (1) effects on bone cell; (2) hormone-like effect; (3) effects on trace element balance; and (4) effects on cytokine.

Table 2 Summary of other ten single herbs

Herbs	Active ingredients	Types	Mechanisms
<i>Corni Fructus</i>	water extract	Type I	to increase fatigue resistance, calcium, phosphorus contents, and density, lower parathyroid hormone level, and inhibit bone resorption (Cui and Chen, 2007)
<i>Cnidii Fructus</i>	osthole	Type I Type II	to increase serum OC level by promoting OB to synthesize and secrete OC (Tang <i>et al.</i> , 2006)
<i>Psoraleae Fructus</i>	acetone extract ethanol extract water solution	Type I	to improve bone metabolism index and serum cytokine levels (Cai and Zhang, 2009); estrogen-like effect (Huang <i>et al.</i> , 2000)
<i>Dipsaci Radix</i>	ethanol extract total glycosides	Type I	to promote the proliferation of OB (Wang, Zhang, and Yang, 2006) and accelerate the ALP secretion (Zhang and Yang, 2008)
<i>Astragali Radix</i>	water extract	Type II	to inhibit bone resorption of OC and promote bone formation (Xie <i>et al.</i> , 1997)
<i>Ginseng Radix et Rhizoma</i>	water solution	Type I	to increase bone mass and trabeculae; to decrease OB count, bone resorption, and turnover rate (Liu <i>et al.</i> , 2003); to have estrogen-like effect (Liao, Newmark, and Zhou, 2002)
<i>Puerariae Lobatae Radix</i>	isoflavone	Type I	to have estrogen-like effect (He, 2008); to inhibit the reduction of trabecular number and thickness; to restore the separation of the trabecular bone growth (Wang <i>et al.</i> , 2003)
<i>Eucommiae Folium</i>	total flavonoids	Type I	to strengthen the proliferation and metabolism of OB <i>in vitro</i> culture (Rao <i>et al.</i> , 2004)
<i>Achyranthis Bidentatae Radix</i>	total saponins	Type II	to accelerate the bone regeneration rate by lowering conversion factor (such as ALP and OC) (Zhang <i>et al.</i> , 2012)
<i>Drynariae Rhizoma</i>	total flavonoids	Type I Type II	to decrease the apoptosis of OB by improving the ratio of Bcl-2 mRNA to Bax mRNA (Huang <i>et al.</i> , 2011)

Compound herbs

The three basic principles for treating OP were proposed in the theory of TCM, such as tonifying kidney to strengthen bone, invigorating spleen to nourish Qi, and activating blood to dredge collaterals (Jin *et al.*, 2007). According to common syndromes, OP could be divided into seven types of diseases (Table 3).

So far, by the most authoritative data reports on using CHM for OP, Xianling Gubao (XLGB) is the first CHM formula which has been approved for the clinical use in accordance with FDA (US) standards by the United States and SYNARC Clinical Research Centers. XLGB is composed of *Epimedii Folium*, *Dipsaci Radix*, *Psoraleae Fructus*, *Rehmanniae Radix Praeparata*, *Salviae Miltiorrhizae Radix et Rhizoma*, and *Anemarrhenae Rhizoma*. Previous studies (Zhu *et al.*, 2012) have shown that bone mineral density of lumbar spine was significantly improved by 2.11% after

treating with XLGB for six months, which was more significant than that in the control group and maintaining hip bone mineral density. In clinical application, other researchers revealed that XLGB could improve the contents of ALP, BGP, and IGF-1. XLGB could also reduce IL-6, TNF- α , and type I collagen levels. So XLGB played a dual role in regulating bone metabolism (Zhang *et al.*, 2004). In addition, XLGB was able to prevent ovariectomized (OVX)-induced deterioration of musculoskeletal tissues at the hip without causing uterine stimulation (Qin *et al.*, 2005). The results showed the following facts: (1) XLGB-treated OVX rats showed no difference compared to the Sham group whereas OVX-induced significant deterioration in variables related to bone density, microarchitecture, and mechanical strength ($P < 0.05$); (2) Biochemical markers showed no difference between Sham and XLGB groups as compared

Table 3 Seven disease types of OP in TCM theory with treatment of common formulas and function

Disease types	Common formulas and compositions	Functions
syndrome of Yin deficiency of liver and kidney	Zuogui Wan: <i>Rehmanniae Radix Praeparata</i> , <i>Dioscoreae Rhizoma</i> , <i>Corni Fructus</i> , <i>Lycii Fructus</i> , <i>Cervi Cornus Colla</i> , <i>Testudinis Cara Pacis et Platri Colla</i> , <i>Cuscutae Semen</i> , <i>Achyranthis Bidentatae Radix</i> , <i>Anemarrhenae Rhizoma</i> , <i>Phellodendri Chinensis Cortex</i>	nourishing Yin to strength bone and replenishing kidney essence (Sun, 2002)
syndrome of Qi deficiency of spleen	Shenlin Baizhu San: <i>Nelumbinis Semen</i> , <i>Coicis Semen</i> , <i>Amomi Fructus</i> , <i>Platycodonis Radix</i> , <i>Lablab Semen Album</i> , <i>Poria</i> , <i>Ginseng Radix et Rhizoma</i> , <i>Glycyrrhizae Radix et Rhizoma</i> , <i>Atractylodis Macrocephalae Rhizoma</i> , <i>Dioscoreae Rhizoma</i> , <i>Citri Reticulatae Pericarpium</i>	invigorating spleen and replenishing Qi, warming and recuperating kidney Yang (Wei, Wang, and Wei, 2001)
syndrome of kidney Yang deficiency	Yougui Wan: <i>Rehmanniae Radix Praeparata</i> , <i>Aconiti Lateralis Radix Praeparata</i> , <i>Cinnamomi Cortex</i> , <i>Dioscoreae Rhizoma</i> , <i>Cuscutae Semen</i> , <i>Cervi Cornus Colla</i> , <i>Lycii Fructus</i> , <i>Eucommiae Folium</i> , <i>Corni Fructus</i> , <i>Angelicae Sinensis Radix</i>	warming kidney to reinforce Yang and relieve superficies syndrome (Liu, 2003)
syndrome of kidney essence deficiency	Heche Dazao Wan: <i>Hominis Placenta</i> , <i>Rehmanniae Radix Praeparata</i> , <i>Eucommiae Folium</i> , <i>Asparagi Radix</i> , <i>Ophiopogonis Radix</i> , <i>Testudinis Cara Pacis et Platri Colla</i> , <i>Phellodendri Chinensis Cortex</i> , <i>Achyranthis Bidentatae Radix</i>	invigorating kidney, replenishing kidney essence and tonifying blood
syndrome of both Qi and blood deficiency	Shiquan Dabu Decoction: <i>Rehmanniae Radix Praeparata</i> , <i>Paeoniae Radix Alba</i> , <i>Angelicae Sinensis Radix</i> , <i>Chuanxiong Rhizoma</i> , <i>Ginseng Radix et Rhizoma</i> , <i>Atractylodis Macrocephalae Rhizom</i> , <i>Poria</i> , <i>Glycyrrhizae Radix et Rhizoma</i> , <i>Praeparata Cum Melle</i> , <i>Astragali Radix</i> , <i>Cinnamomi Cortex</i>	invigorating Qi and strengthening the spleen to nourish the blood
syndrome of Qi stagnation and blood stasis	Shentong Zhuyu Decoction: <i>Gentianae Macrophyllae Radix</i> , <i>Chuanxiong Rhizoma</i> , <i>Persicae Semen</i> , <i>Carthami Flos</i> , <i>Glycyrrhizae Radix et Rhizoma</i> , <i>Notopterygii Rhizoma et Radix</i> , <i>Myrrha</i> , <i>Cyperii Rhizoma</i> , <i>Togopteri Faeces</i> , <i>Achyranthis Bidentatae Radix</i> , <i>Pheretima</i> , <i>Angelicae Sinensis Radix</i>	activating Qi and promoting blood circulation for removing blood stasis (Liu, 2003)
exogenous wind syndrome	Fangfeng Decoction: <i>Saposhnikoviae Radix</i> , <i>Ephedrae Herba</i> , <i>Angelicae Sinensis Radix</i> , <i>Gentianae Macrophyllae Radix</i> , <i>Cinnamomi Cortex</i> , <i>Puerariae Lobatae Radix</i> , <i>Poria</i> , <i>Zingiberis Rhizoma Recens</i> , <i>Jujubae Fructus</i> , <i>Glycyrrhizae Radix et Rhizoma</i>	dispelling pathogenic wind, dredging channel blockade and relieving pain

with the higher bone turnover in OVX rats ($P < 0.05$); (3) mRNA expressions of MHC-I Ila and I Ib were down-regulated in OVX rats but up-regulated by XLGB treatment ($P < 0.05$); (4) As compared with the OVX group, no uterine hypertrophy was found in XLGB-treated rats.

Over the past years, a number of studies have emerged besides XLGB to better reveal the therapeutic effects of CHM on the treatment of OP.

A triple herbal product Buguling, composed of *Epimedii Folium*, *Psoraleae Fructus*, and *Ligustri Lucidi Fructus*, increased the spine BMD by 0.69%, the hip BMD by 0.21%, and the tibia strength strain index by 1.94% in the subjects which were more than 10 years after menopause (Leung, Cheng, and Chan, 2011).

Saikokaryukotsuboreito is a traditional Japanese herbal remedy composed of *Os Draconis*, *Bupleuri Radix*, *Zingiberis Rhizoma Recens*, *Ostreae Concha*, *Rhei Radix et Rhizoma*, *Jujubae Fructus*, *Poria*, *Cinnamomi Ramulus*, *Ginseng Radix et Rhizoma*, and *Scutellariae Radix*. Saikokaryukotsuboreito could prevent loss of bone volume and suppress serum IL-6 level in the postmenopausal model (Hattori *et al*, 2010).

Conclusion

The single herbs or compound herbs described are only the representatives of diversified CHM. According to the information collected in this paper, it could be concluded that herbs with kidney-tonifying, spleen-tonifying, or stasis-removing effects all have potential to be used in treating OP. The treatment with CHM is comprehensive and integrated. When treating OP, most of the herbal medicines used are sweet in flavor and warm in nature with an effect of nourishing the liver and kidney. Compound herbs with different specialties and various compatibilities are applied under the guidance of the principles of tonifying kidney and liver, strengthening spleen and Qi, and activating blood to remove stasis, which could improve the clinical symptoms of OP and the life quality of patients. In brief, the effects of CHM on OP are manifest.

At present, several problems are still unsolved on CHM in the treatment and prevention of OP. Extensive and in-depth studies are required to focus on the action mechanism owing to the complicated constituents in compound herbs. The treatment of secondary OP and

male OP requires further attention. Further explorations on the rational compatibilities of CHM are expected. Standards on syndrome differentiation, diagnosis, and treatment of OP and the efficacy of CHM need to be unified. Large sample studies on randomized, placebo-controlled, and double-blind trials are urged to be supplemented. Long-term observations on the treatment of OP with CHM are to be conducted and reported. More biological researches on OP are required. All the problems above are worth being further discussed.

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