



Prevention and Treatment of Osteoporosis with Traditional Chinese Medicine Gushukang

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Authors' contributions

This work was carried out in collaboration among all authors. Author JW searched literatures and concepted and finalized the manuscript. Authors JSX, JW and RHZ searched literatures and discussed and wrote the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

As our population continues to age, osteoporosis is becoming more common and burdensome for society. Its treatment is troublesome because its mechanism is complicated and easily hidden behind other ailments and symptoms. In addition, the adverse effect of traditional therapeutic drugs for osteoporosis is another puzzle for both clinicians and patients. The Traditional Chinese Medicine (TCM) known as Gushukang (GSK) has a long history in treating osteoporosis. However, because the formulation of GSK consists of multiple plant products, it is difficult to determine its proper purity, efficacy, dosage, and safety as required by modern medicine. Still, researchers have begun to use modern scientific tools to investigate GSK for treating osteoporosis. Following the inclusion of TCM in the latest *International Statistical Classification of Diseases and Related Health Problems (ICD-11, 2019)* by the WHO and recent elucidation of the therapeutic mechanisms of GSK in treating diseases, it has been demonstrated that GSK does indeed show potential for treating osteoporosis in the future. This review summarizes recent advances surrounding GSK for the treatment of osteoporosis in both laboratory animals and humans, from complex formulae to single ingredients.

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1. INTRODUCTION

Osteoporosis is a type of disorder characterized by a decrease in bone mineral density (BMD) due to alterations of the bone microstructure under the effects of multiple factors. The symptoms of osteoporosis can vary from osteoporotic pain, fracture to disability [1,2]. It puts patients at high risk of bone fractures and can be life-threatening. Osteoporosis classifications include both primary osteoporosis such as postmenopausal osteoporosis in women and senile osteoporosis in the elderly [3] and secondary osteoporosis which can be induced by some diseases such as hyperparathyroidism, diabetes, and cancer –as well as some medications and surgery treatments [4]. With the entry of an aged era, osteoporosis is becoming a more prominent social problem [5]. However, the treatment of osteoporosis poses difficulties for both society and clinicians because it is often first discovered as a comorbid with other diseases and the mechanisms affecting the body are relatively complicated [2]. Since osteoporosis is caused by the decrease in BMD, the fundamental therapeutic approach should aim to increase the bone formation, osteogenesis.

The current generation of drugs for the treatment of osteoporosis have a wide range of adverse effects, which has driven researchers to seek alternative methods of treatment, with particular interest in Chinese herbal medicines [3]. In a population-based study of 16,544 patients with osteoporosis in Taiwan, 70% of them were prescribed traditional Chinese medicine (TCM), suggesting that it is common practice to prescribe TCM to treat osteoporosis [6]. Previous studies have also demonstrated that TCM can significantly decrease the fracture ratio in osteoporotic patients [7,8], and a clinical study of 56 patients suffering osteoporotic lower back pain showed that TCM provided effective pain relief [9]. These results suggest that TCM is worthy of further study of its application in treating osteoporosis.

Gushukang (GSK) is one formulation of TCM. Its fundamental components are *Herba Epimedii*, *Radix Rehmanniae Preparata*, *Rhizoma Drynariae*, *Radix Astragali*, *Radix Salviae Miltiorrhizae*, *Auricularia*, and *Semen Cucumidissativi* (Fig. 1) [10,11]. GSK is widely used throughout China, Japan, and Korea to treat osteoporosis. However, purity, dosage, and

safety standard have not been established, and its mechanism and efficacy are not fully understood. As a result, though it shows promise as an osteoporosis treatment, it has not seen worldwide recognition or adoption. The listing of TCM in the latest version of the *International Statistical Classification of Diseases and Related Health Problems* by the WHO (ICD-11 version, 2019) has brought renewed attention to TCM, including GSK as a treatment for osteoporosis, and it has spurred the application of modern pharmaceutical science techniques in understanding these traditional remedies.

2. EFFECTS OF GSK IN TREATING OSTEOPOROSIS

Based on the clinical practice in a long history and experimental results performed in China, GSK has been listed as the basic prescription for treating primary osteoporosis [12]. However, there are very few English publications on GSK in treating osteoporotic patients and there is no consensus on standards for purity, dosage, or safety. In a study of primary osteoporosis in men over 70 years of age and post-menopausal women, GSK was shown to increase the levels of estrogen and androgen, which in turn slowed down bone density decay or even increased bone mineral density [13]. In animal models of primary osteoporosis in aged mice, GSK significantly improved trabecular micro-architecture and bone mass, increasing the maximal bending load and elastic modulus of their bones [10]. Similar results were found in a secondary osteoporosis model of mice, induced by ovariectomy (OVX) [11,14]. In hens reaching the timed point of egg-laying cycle, GSK has been shown to promote egg-laying rate, improve bone characteristics, and prevent bone loss [15]. In adult mice, GSK can promote bone formation and inhibit bone resorption, resulting in an overall increase of bone mass [16].

Some ingredients of GSK have also demonstrated protection against osteoporosis when applied individually. Icarrin, an active ingredient of the herb *Epimedii*, a component of GSK, has been demonstrated to prevent bone loss from iron overload-induced secondary osteoporosis [17] and to promote osteogenesis in rats with OVX [18]. Extract from *Rhizoma Drynariae*, another herbal component of GSK, also showed anti-osteoporotic effects in retinoic acid-induced secondary osteoporosis [19].

3. MECHANISM OF GSK IN TREATING OSTEOPOROSIS

Because GSK is a complex formula composed of several herbs, its mechanism of effect is complicated and targets multiple signaling pathways simultaneously.

3.1 GSK Modulates Mineral Metabolism

Calcium homeostasis is important for the normal functioning of bones, and its disturbance plays an important role in osteoporosis. GSK significantly increases the levels of serum calcium and the bone density of mice subjected to OVX and simultaneously significantly decreases the level of urinary calcium. This modulation of calcium homeostasis by GSK is related to its enhancing effects on serum 25-hydroxyvitamin D, mRNA expression of calcium-binding protein-28k and vitamin D receptor in the kidneys, and mRNA expression of claudin-16 in the duodenum. At the same time, GSK decreases the expression of claudin-14 mRNA [20]. In an aged mice primary osteoporosis model, GSK significantly increased the serum levels of 25-OH-D and 1,25-OH₂-D. GSK also improved calcium homeostasis by increasing the expression of transient receptor potential cation channel subfamily V member 6 (TRPV6) in the duodenum and TRPV5 in the kidneys, while decreasing the expression of claudin-14 in duodenum and kidneys, resulting in an increase of serum calcium and a decrease of calcium in urine [10].

3.2 GSK Modulates Osteogenesis

As a mineral salt disorder, osteoporosis may be due to the imbalance between osteoblast and osteoclast activity. GSK can inhibit the apoptosis of osteocytes by enhancing the activity of the gene Bcl-xL and decreasing the activity of BAK [11]. In another study, GSK was found to inhibit osteoclastogenesis in bone marrow macrophages (BMMs) activated by signals from the receptor activator of nuclear factor kappa-B ligand (RANKL) in rats with OVX. Conversely, GSK can enhance osteoblastogenesis by stimulating the expression of Col-1, Osteocalcin, and alkaline phosphatase (ALP) [14]. This stimulation is achieved through the modulation of several factors, including the nuclear factor of activated T-cells cytoplasmic1 (NFATC1), c-Fos, matrix metalloproteinase 9 (MMP9), cathepsin K (Ctsk), TRAP, carbonic anhydrase II (Car2), Osteix, and Runt-related transcription factor 2

(RUNX2) [14]. In adult mice, GSK can enhance the differentiation of osteoblasts and suppress the differentiation of osteoclasts, resulting in an increase of bone mass. This effect may be related with the formation of type-H vessels in mice through up-regulating the expression of hypoxia inducible factor-1 (HIF-1 α) [16]. The GSK ingredient Icarrinon its own has also been shown to promote osteogenesis and angiogenesis of BMSCs in rats with OVX [18].

3.3 Other Signaling Pathways

As discussed, the RANKL signaling pathway is involved in calcium modulation, but RANKL also activates mitogen-activated protein kinase (MAPK) and nuclear factor of activated T-cells 1 (NFATC1), both of which reduce BMD via another route. GSK can enhance calcium signaling by Arctiin (ARC), which has been shown to inhibit RANKL activity and subsequently prevent bone loss in an OVX-induced mouse model of osteoporosis [21].

Additionally, GSK can modulate osteoporosis at the transcriptional level. In a secondary osteoporosis model of OVX rats, GSK was able to prevent osteoporosis and decrease the risk of trabecular fracture by increasing the levels of bone marrow macrophages 2 (BMP-2) and RUNX2 [11]. Icarrin, an active ingredient of GSK, has been shown to prevent bone loss by both weakening mitochondrial function [22] and promoting osteogenesis by stimulating mesenchymal stem cell differentiation through the RUNX2 and BMP-2 signaling pathways [23].

4. PROSPECTS OF GSK IN TREATING OSTEOPOROSIS

Recently, some modern scientific strategies have been used in the study of osteoporosis with GSK. For example, bioinformatics was applied to analyze the effective ingredients of *Rhizoma Drynariae* which is one herbal component of GSK and identified 16 active ingredients and 7 key targets in treating osteoporosis [24]. High performance liquid chromatography-mass spectroscopy (HPLC-MS) was used to analyze the herbal components of GSK, *Epimedii* and *Rhizoma Drynariae*, identifying 16 extracted chemicals from *Epimedii* which promoted osteogenesis of mesenchymal stem cells [17] and 21 osteoporosis biomarkers which were regulated by *Rhizoma Drynariae* [19]. Following similar rigorous strategies, the purity, efficacy, dosage, and safety requirements demanded by



Fig. 1. The herbal components used in the formulation of GSK

modern medical standards can be investigated according to the requirements of Western medicine, the mechanism of GSK will be clarified, which will facilitate the future application of GSK in treating osteoporosis.

5. CONCLUSION

The TCM formula GSK had demonstrated potential in treating osteoporosis in both experimental models and clinical practice. Modern techniques are being applied to elucidate its active components and functional mechanisms and to assess the purity, dosages, and safety standards required by modern medicine. Following the elucidation of the complicated mechanism of GSK with modern approaches, GSK is on track to be accepted more broadly and may finally be applied toward the treatment of osteoporosis worldwide.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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