


# Efficacy and safety of Chinese herbal medicine Buzhong Yiqi decoction for postmenopausal women with osteoporosis

## A protocol for systematic review and meta-analysis

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### Abstract

**Background:** Postmenopausal osteoporosis (PMOP) is a disorder of bone metabolism caused by estrogen deficiency in women after menopause, which manifests clinically as pain, spinal deformities, and even fragility fractures, affecting the quality of life of patients and possibly shortening their life span. Traditional Chinese medicine prescription Buzhong Yiqi Decoction (BZYQD) has been widely used in clinical practice and achieved good results. But there is no high-level evidence to support this result. The aim of this study is to evaluate BZYQD's efficacy and safety in the management of PMOP.

**Methods:** We will search articles in 7 electronic databases including Chinese National Knowledge Infrastructure, Wanfang Data, Chinese Scientific Journals Database, Chinese databases SinoMed, PubMed, Embase, and Cochrane Library databases. All the publications, with no time restrictions, will be searched without any restriction on language and status, the time from the establishment of the database to September 2022. Two reviewers will independently assess the quality of the selected studies, NoteExpress and Excel software will be used to extract data, and the content will be stored in an electronic chart. Different researchers will separately screen the titles and abstracts of records acquired potential eligibility which comes from the electronic databases. Full-text screening and data extraction will be conducted afterward independently. Statistical analysis will be conducted using RevMan 5.4 software.

**Results:** This study will evaluate the efficacy and safety of BZYQD in the treatment of PMOP, to provide high-quality, evidence-based clinical recommendations.

**Conclusion:** The study provides a trustable clinical foundation for BZYQD in the treatment of PMOP.

**Abbreviations:** BZYQD = Buzhong Yiqi Decoction, PMOP = postmenopausal osteoporosis, RCTs = randomized controlled trials.

**Keywords:** Buzhong Yiqi Decoction, postmenopausal osteoporosis, protocol

## 1. Introduction

Postmenopausal osteoporosis (PMOP) refers specifically to a group of primary diseases in postmenopausal women who develop bone cortical thinning, increased porosity, thinning and perforation of bone trabeculae, increased bone fragility, and increased incidence of fracture risk due to disturbances in estrogen metabolism.<sup>[1,2]</sup> Studies have shown that postmenopausal

women have a lifetime probability of osteoporotic fractures of up to 50%.<sup>[3]</sup> The spine and hip are the preferred sites for osteoporotic fractures, and the mortality rate is high in elderly women after the occurrence of these osteoporotic fractures because most of them are accompanied by their own underlying diseases and the need for long-term bed rest, which seriously threatens the quality of life of women. It increases the social and economic burden.<sup>[4,5]</sup>

K-MX and J-FY contributed equally to this work.

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The datasets generated during and/or analyzed during the current study are publicly available.

The authors have no ethical statement to disclose.

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Although there are many causes of primary osteoporosis, postmenopausal estrogen deficiency is an important cause of osteoporosis in women, and the bone marrow environment releases a variety of cytokines, such as Tumor Necrosis Factor- $\alpha$ , Interleukin-1, Interleukin-6, and Receptor Activator Nuclear Kappa-b Ligand, which stimulate and exacerbate bone resorption.<sup>[6]</sup>

Low back pain and spinal deformity are common manifestations of osteoporosis, but the disabling and mortality of osteoporotic fractures of the hip and spinal vertebrae remain the greatest hazard.<sup>[7,8]</sup>

Traditional Chinese medicine believes that spleen deficiency is the key to the pathogenesis of osteoporosis, and to a certain extent, spleen deficiency contributes to the occurrence and development of osteoporosis, so the method of benefiting qi and strengthening the spleen is an important treatment to prevent and treat osteoporosis.<sup>[9,10]</sup> The traditional formula Buzhong Yiqi Decoction (BZYQD) was recorded in “Treatise on Internal and External Injuries and Confusion,” which is a classic Chinese medicine book, and is a classic formula for tonifying the spleen and benefiting the qi. It is composed of 8 traditional Chinese medicines: Radix Astragali (Zhi Huang Qi), ginseng (Ren Shen), angelica sinensis (Dang Gui), tangerine peel (Chen Pi), cimicifuga foetida (Sheng Ma), bupleurum (Chai Hu), fried atractylodes (Chao Bai Zhu), and baked licorice (Zhi Gan Cao).<sup>[11–13]</sup> Studies have shown that BZYQD can effectively improve bone metabolic indexes in PMOP, and effectively increase bone mass and significantly inhibit osteoclast activity, thereby enhancing BMD T values.<sup>[14,15]</sup>

Currently, many scholars are convinced that BZYQD can enhance BMD T values and effectively alleviate and improve the symptoms of PMOP patients. However, there is no evidence-based medical evidence to support the safety and efficacy of BZYQD in the treatment of PMOP, and the purpose of this study is to provide a reliable basis for clinical selection.

## 2. Methods

### 2.1. Study registration

This protocol report is structured according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis Protocols statement.<sup>[16]</sup> It is registered on the International Prospective Register of Systematic Reviews. (Registration number: CRD42022365367)

### 2.2. Inclusion criteria

**2.2.1. Type of study.** Only randomized controlled trials (RCTs) will be included irrespective of blinding, publication status, or language in this study.

**2.2.2. Types of participants.** Patients were diagnosed with postmenopausal osteoporosis and the study belongs to a randomized controlled trial. Clinical results included Lumbar vertebral and Femoral neck bone density (dual-energy X-ray absorptiometry); visual analog pain (VAS) score; Serum bone metabolic markers; incidence of fragility fractures; Quality of life and adverse effects. The experimental group must contain BZYQD or modified BZYQD and the control group was not limited except that. Otherwise, studies will be excluded if they cannot meet the inclusion criteria.

**2.2.3. Types of interventions.** Interventions of the experimental group are BZYQD or modified BZYQD. There are no restrictions on the way of administration, dosage, and treatment period.

**2.2.4. Types of control groups.** The control group has other treatment methods different from BZYQD or modified BZYQD.

### 2.2.5. Outcomes.

**2.2.5.1. Primary outcome measures.** The primary outcome is Lumbar vertebral and Femoral neck bone density (dual-energy X-ray absorptiometry).

**2.2.5.2. Secondary outcomes.** The secondary outcome is visual analog pain (VAS) score; Serum bone metabolic markers; incidence of fragility fractures; Quality of life and adverse effects.

### 2.3. Search strategy

Chinese National Knowledge Infrastructure, Wanfang, Chinese Scientific Journals Database, Chinese databases SinoMed, PubMed, Embase, and Cochrane Library databases were searched for this study. Take the subject terms combined with free words to search, take PubMed as an example: terms consist of (osteoporosis OR postmenopausal osteoporosis) AND (BZYQD OR Buzhong Yiqi Tang OR modified BZYQD) AND (randomized controlled trial OR controlled clinical trial OR random trials). The searches will be conducted by 2 authors independently (YJF and XKM) as shown in Table 1.

### 2.4. Data collection and analysis

**2.4.1. Selection of studies.** Different researchers (ZX and HHM) will separately screen the titles and abstracts of records acquired potential eligibility which comes from the electronic databases. The obtained literature is managed by Notoexpress, irrelevant and duplicate articles are excluded by reading the title and abstract, Full texts screening and data extraction will be conducted afterward independently, and finally selected according to the inclusion criteria, Any disagreement will be resolved by discussion with the third author (CLM) until consensus is reached or by consulting a third author. Preferred Reporting Items for Systematic Reviews and Meta-analysis Protocols flowchart will be used to show the selection procedure (Fig. 1).

**2.4.2. Data extraction and management.** NoteExpress and Excel software will be used to extract data, and the content will be stored in an electronic chart. The following data will be extracted: author, year of publication, country, interventions of experimental groups and control groups, time point, outcome measures, age of patients, the total number of people included in the study, patients' basic information, etc. Different researchers will separately extract data. Any disagreement regarding data

**Table 1**  
pubmed database search strategy.

Search number	Items
1	"Postmenopausal osteoporosis" [Mesh]
2	Postmenopausal osteoporosis [Title/Abstract]
3	Osteoporosis [Title/Abstract]
4	1 OR 2 OR 3
5	BZYQD [Title/Abstract]
6	Buzhong Yiqi Tang [Title/Abstract]
7	Modified BZYQD [Title/Abstract]
8	5 OR 6 OR 7
9	Randomized controlled trial [Title/Abstract]
10	Controlled clinical trial [Title/Abstract]
11	Random trials [Title/Abstract]
12	9 OR 10 OR 11
13	4 AND 8 AND 12

BZYQD = Buzhong Yiqi decoction.

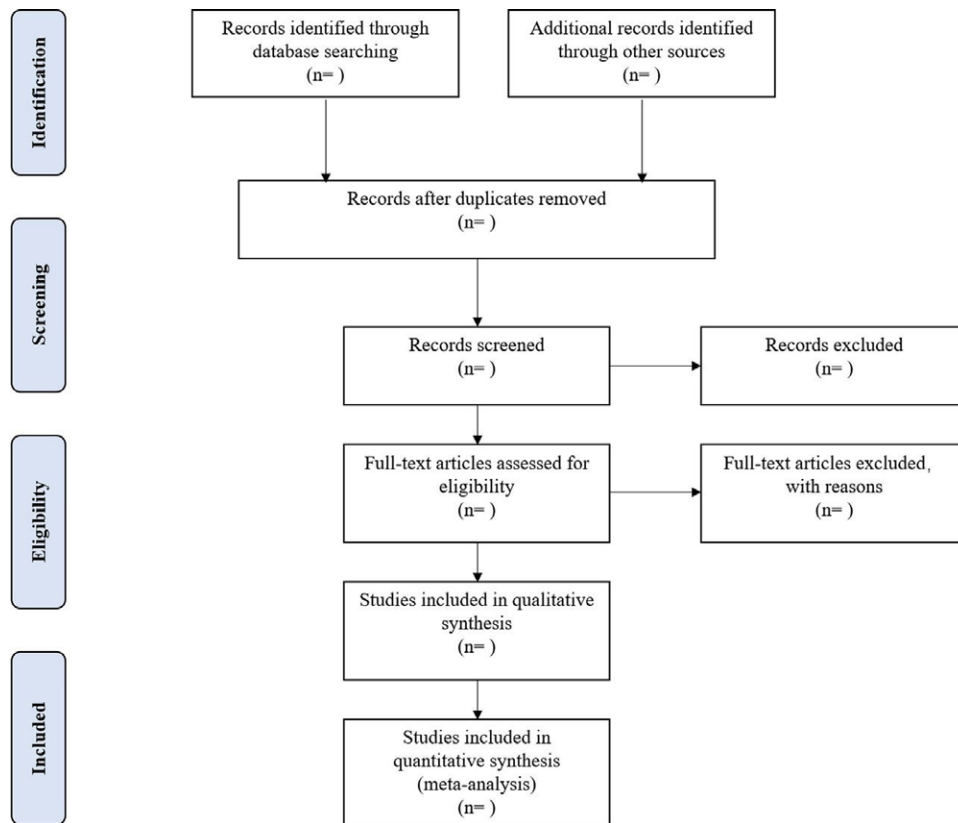


Figure 1. Flowchart of literature selection.

extraction will be resolved by discussion until consensus is reached or by consulting a third author.

### 2.5. Risk of bias assessment

Two reviewers (LJL and XKM) will independently assess the quality of the selected studies according to the Cochrane Collaboration's tool for RCTs.<sup>[17]</sup> Items will be evaluated in 3 categories: Low risk of bias, unclear bias, and high risk of bias. The following characteristics will be evaluated: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other biases. Results from these questions will be graphed and assessed using Review Manager 5.4 (Cochrane Collaboration, London, UK). The results will be presented in the form of a graph and will be independently evaluated by 2 researchers (LJL and XKM). If there are differences of opinion, they will be discussed with the third researcher (YJF).

### 2.6. Statistical analysis

Statistical analysis will be conducted using RevMan 5.4 software (Cochrane Collaboration). For continuous data, will be used mean difference (MD) as the effect indicator with a 95% confidence interval, and dichotomous data will be calculated as risk ratio (RR) or odds ratio (OR) as the effect index with a 95% confidence interval. The  $I^2$  statistic will be used to assess levels of the heterogeneity, when  $I^2 < 50\%$ , the fixed-effect model can be used for analysis, otherwise, the random-effect model will be used.

### 2.7. Sensitivity analysis and subgroup analysis.

We will consider the subgroup analysis intervention of the experimental group. In addition, Through sensitivity analysis

assess the source of heterogeneity, by excluding low-quality studies, or by excluding 1 of the included studies in turn, if there is no significant change in the heterogeneity, the results are robust, otherwise, the excluded study may be the heterogeneous originate.

### 2.8. Publication bias

In this study, less than 10 RCTs will use funnel plots to evaluate publication bias, or else, Egger's regression test will be used.

## 3. Discussion

The use of BZYQD in the treatment of PMOP in women has been historically proven to be effective and can help improve patients' symptoms, but there has been no high-level clinical evidence-based basis to convince the academic community. The purpose of this study is to address this concern to provide an evidence-based basis for clinical decision-making.

### Author contributions

**Conceptualization:** Kemeng Xiang, Huiming Hou, Jinlei Li.

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**Funding acquisition:** Limin Chen, Jinlei Li.

**Investigation:** Weitong Liu, Xing Zhou.

**Methodology:** Kemeng Xiang, Huiming Hou.

**Resources:** Xing Zhou.

**Software:** Kemeng Xiang.

**Supervision:** Jingfan Yang.

**Validation:** Jingfan Yang.

**Writing – original draft:** Kemeng Xiang, Jinlei Li.

**Writing – review & editing:** Jingfan Yang, Xing Zhou.

## References

- [1] Kanis JA, Cooper C, Rizzoli R, et al. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. *Osteoporos Int*. 2019;30:3–44.
- [2] Seeman E. Age- and menopause-related bone loss compromise cortical and trabecular microstructure. *J Gerontol A Biol Sci Med Sci*. 2013;68:1218–25.
- [3] Lippuner K, Johansson H, Kanis JA, et al. Remaining lifetime and absolute 10-year probabilities of osteoporotic fracture in Swiss men and women. *Osteoporos Int*. 2009;20:1131–40.
- [4] Schürch MA, Rizzoli R, Mermillod B, et al. A prospective study on socioeconomic aspects of fracture of the proximal femur. *J Bone Miner Res*. 1996;11:1935–42.
- [5] Trombetti A, Herrmann F, Hoffmeyer P, et al. Survival and potential years of life lost after hip fracture in men and age-matched women. *Osteoporos Int*. 2002;13:731–7.
- [6] Kular J, Tickner J, Chim SM, et al. An overview of the regulation of bone remodelling at the cellular level. *Clin Biochem*. 2012;45:863–73.
- [7] Biver E, Ferrari S. Ostéoporose [Osteoporosis]. *Rev Med Suisse*. 2020;16:78–80.
- [8] Aspray TJ, Hill TR. Osteoporosis and the Ageing Skeleton. *Subcell Biochem*. 2019;91:453–76.
- [9] An J, Yang H, Zhang Q, et al. Natural products for treatment of osteoporosis: The effects and mechanisms on promoting osteoblast-mediated bone formation. *Life Sci*. 2016;147:46–58.
- [10] Zhao Y, Qiu J, Chen T, et al. The efficacy and safety of traditional Chinese medicine's tonifying-kidney, strengthening-spleen, and invigorating-blood circulation (Bushen-Jianpi-Huoxue) principle for type 2 diabetes mellitus with osteoporosis: A protocol for systematic review and meta-analysis. *Medicine (Baltim)*. 2021;100:e25197.
- [11] Xie Y, Fan Y, Yang C, et al. Efficacy and safety of Buzhong Yiqi decoction combined with surgery for rectal prolapse: a protocol for systematic review and meta analysis. *Medicine (Baltim)*. 2020;99:e22732.
- [12] Wang Y, Zhang Y, Liu Z, et al. Effects of Buzhong Yiqi decoction combined with THP bladder perfusion on postoperative efficacy in patients with bladder cancer. *Evid Based Complement Alternat Med*. 2021;2021:3685213.
- [13] Lu B, Du J, Wu X. The effects of modified Buzhong Yiqi decoction combined with Gangtai ointment on the wound healing and anal function in circumferential mixed hemorrhoid patients. *Am J Transl Res*. 2021;13:8294–301.
- [14] Hu B, An HM, Shen KP. Pharmacological study of Buzhong Yiqi Decoction: a review. *Zhong Xi Yi Jie He Xue Bao*. 2008 Jul;6:752–5.
- [15] Chen DF, Li X, Xu Z, et al. Hexadecanoic acid from Buzhong Yiqi decoction induced proliferation of bone marrow mesenchymal stem cells. *J Med Food*. 2010;13:967–70.
- [16] Stewart LA, Clarke M, Rovers M, et al. Preferred reporting items for systematic review and meta-analyses of individual participant data: the PRISMA-IPD statement. *JAMA*. 2015;313:1657–65.
- [17] Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.