INPLASY

Natural products, herbal medicines, and nutraceuticals as adjunctive therapies for compression fractures: a protocol for a systematic review and Bayesian network meta-analysis

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ADMINISTRATIVE INFORMATION

Support - No support.

Review Stage at time of this submission - The review has not yet started.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 21 August 2026 and was last updated on 21 August 2026.

INTRODUCTION

Review question / Objective To evaluate and compare the efficacy and safety of herbal medicines, natural products, and nutraceuticals used as adjunctive therapies in adults with osteoporotic vertebral compression fractures (OVCFs) receiving conventional treatment. This review will address the following question: among adults with OVCF managed conservatively, what are the comparative effects of adjunctive herbal medicines, natural products, and nutraceuticals on pain, physical function, quality of life, bone-related outcomes, subsequent vertebral fractures, and adverse events?
Conventional pharmaceutical osteoporosis treatments, including calcium and vitamin D supplementation, will be considered background therapies rather than eligible experimental interventions. Where a connected evidence network is available, a Bayesian network meta-analysis will be conducted to estimate the relative effects of eligible adjunctive interventions.

Rationale Osteoporotic vertebral compression fractures (OVCFs) are common complications of osteoporosis and can result in acute or persistent pain, functional impairment, reduced mobility and quality of life, progressive vertebral deformity, and an increased risk of subsequent fractures. For patients who do not require vertebral augmentation or surgical intervention, conventional conservative management typically consists of analgesics, anti-osteoporosis pharmacotherapy, calcium and vitamin D supplementation, bracing, activity modification, and rehabilitation. However, these treatments do not always provide adequate symptom relief or functional recovery, and some pharmacological treatments may be limited by adverse effects, contraindications, or delayed therapeutic effects.
Consequently, complementary and alternative interventions, including herbal medicines, natural products, and nutraceuticals, are used alongside conventional treatment with the aim of improving pain, physical function, bone health, and overall recovery. Such adjunctive approaches may be particularly relevant to patients seeking additional

therapeutic options when conventional conservative management alone provides insufficient benefit.

A growing number of randomized controlled trials have evaluated these interventions as adjunctive treatments for OVCF. However, these trials are generally small, investigate heterogeneous interventions, and predominantly compare an individual adjunctive treatment plus conventional care with conventional care alone. Evidence based on the direct head-to-head comparisons among different adjunctive interventions are therefore has not been established yet.

Previous systematic reviews and network meta-analyses have mainly focused on general conservative interventions, conventional pharmacological therapies, postoperative treatments following vertebral augmentation, or broader populations with osteoporosis or osteoporotic fractures. To our knowledge, no systematic review has comprehensively compared the efficacy and safety of herbal medicines, natural products, and nutraceuticals specifically as adjunctive therapies for conservatively managed OVCF.

Therefore, this systematic review and Bayesian network meta-analysis will synthesize direct and indirect evidence to estimate the comparative efficacy and safety of these adjunctive interventions and to determine which treatments may provide the greatest additional benefit when combined with conventional non-surgical care.

Condition being studied Osteoporotic vertebral compression fracture (OVCF) is a fragility fracture of the vertebral body occurring primarily as a consequence of reduced bone strength associated with osteoporosis. It commonly affects older adults and may occur after minimal trauma or without an identifiable traumatic event.

OVCF may cause acute back pain, impaired mobility, limitations in activities of daily living, progressive vertebral height loss and kyphotic deformity, and reduced health-related quality of life. Patients with an OVCF are also at increased risk of subsequent vertebral and other osteoporotic fractures.

METHODS

Search strategy The following electronic databases will be searched from inception to the date of the final search: MEDLINE via PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, China National Knowledge Infrastructure (CNKI), and relevant Korean databases including OASIS.

Search terms will combine controlled vocabulary and free-text terms related to:

(1) osteoporotic vertebral compression fracture, including “vertebral compression fracture,” “vertebral fracture,” “osteoporotic vertebral fracture,” and “osteoporotic compression fracture”;

(2) herbal medicines, including “herbal medicine,” “Chinese herbal medicine,” “traditional medicine,” “phytotherapy,” “herbal formula,” and names of individual herbal preparations;

(3) natural products and nutraceuticals, including “natural product,” “botanical,” “plant extract,” “nutraceutical,” and related terms.

No language restriction will be applied. Reference lists of included studies and relevant systematic reviews and trial registries will also be searched.

Participant or population Adults aged 18 years or older with a diagnosis of osteoporotic vertebral compression fracture or osteoporotic vertebral fracture confirmed radiologically will be eligible. Studies including mixed populations will be eligible only when data for patients with osteoporotic vertebral compression fractures can be extracted separately. Studies focused primarily on traumatic vertebral fractures, malignant or metastatic pathological fractures, infectious fractures, or fractures caused by conditions other than osteoporosis will be excluded.

Intervention Eligible interventions will include herbal medicines, herbal formulas, standardized herbal products or extracts, natural products, nutraceuticals, and nutritional or dietary supplements administered as adjunctive treatment to conventional non-surgical management.Interventions may be used alone as an adjunct or in combination with other eligible complementary interventions. Oral or systemic preparations will primarily be considered. Individual interventions will be treated as separate network nodes where sufficient data are available.

Comparator Eligible comparators will include conventional or usual non-surgical treatment alone, placebo plus conventional treatment, or conventional treatment combined with another eligible herbal, natural-product, or nutritional intervention.The comparability of background conventional treatments will be carefully assessed because differences in concomitant anti-osteoporosis medication, analgesics, calcium/vitamin D, bracing, or rehabilitation may influence the validity of indirect comparisons.

Study designs to be included Randomized controlled trials with parallel-group designs will be

included. Cluster-randomized trials will be eligible if appropriate adjustment for clustering is possible. Quasi-randomized studies, non-randomized comparative studies, observational studies, case series, case reports, and single-arm studies will be excluded.

Eligibility criteria Studies will be included if they:1. include adults with osteoporotic vertebral compression fractures;2. evaluate an eligible herbal medicine, natural product, nutraceutical, or nutritional/dietary supplement as an adjunct to non-surgical conventional treatment;3. use conventional treatment alone, placebo plus conventional treatment, or another eligible adjunctive intervention as the comparator. Studies will be excluded if the principal population has traumatic, malignant, infectious, or other non-osteoporotic vertebral fractures. Complex traditional medicine interventions involving acupuncture, manual therapy, external devices, or rehabilitation without a separable pharmacological, herbal, natural-product, or nutritional component will be excluded.For multi-arm studies, all relevant eligible arms will be extracted.

Information sources MEDLINE via PubMed, Embase, CENTRAL, Web of Science, CNKI, and OASIS will be searched from inception.
WHO International Clinical Trials Registry Platformwill be searched for ongoing or unpublished trials where feasible.
Reference lists of included studies and relevant systematic reviews will be screened. Forward citation searching will also be performed for key eligible studies.
Study authors may be contacted when outcome data, methodological information, or clarification concerning study eligibility is required.

Main outcome(s) The primary outcomes will be:
1. Pain intensity, measured using a validated scale such as the visual analogue scale (VAS) or numerical rating scale (NRS).
2. Physical function or disability, measured using validated instruments, with the Oswestry Disability Index (ODI) preferred where available.
Outcomes will be analyzed according to clinically relevant follow-up periods, provisionally categorized as short term (≤4 weeks), intermediate term (>4 weeks to 3 months), and longer term (>3 months). Where multiple assessments occur within a time window, the assessment closest to the prespecified time point will be used.
For continuous outcomes, mean differences or standardized mean differences with 95% credible intervals will be estimated, as appropriate.

Additional outcome(s) Secondary outcomes will include:
- health-related quality of life;
- bone mineral density;
- radiographic fracture healing or union;
- vertebral height loss or restoration;
- progressive vertebral body collapse;
- Cobb angle or kyphotic deformity;
- subsequent or new vertebral fractures;
- other subsequent osteoporotic fractures;
- use of rescue analgesics;
- need for subsequent vertebroplasty, kyphoplasty, or surgery;
- treatment discontinuation;
- adverse events; and
- serious adverse events.

For binary outcomes, relative risks or odds ratios with 95% credible intervals will be calculated as appropriate. Time-to-event outcomes will be analyzed using hazard ratios when sufficiently reported.

Data management Search records will be imported into reference-management and systematic-review software, and duplicates will be removed.
Two reviewers will independently screen titles and abstracts, assess potentially eligible full-text reports, and extract data using a standardized and piloted data extraction form. Disagreements will be resolved through discussion or consultation with a third reviewer.
Extracted information will include study characteristics, participant characteristics, diagnostic criteria, intervention details, comparator treatments, background conventional therapies, treatment duration, follow-up, outcome data, adverse events, funding, and relevant methodological characteristics.
Multiple reports of the same trial will be linked and treated as a single study.
Data used for statistical analysis will be checked independently before analysis.

Quality assessment / Risk of bias analysis Two reviewers will independently assess risk of bias in included randomized controlled trials using the Cochrane Risk of Bias 2 (RoB 2) tool.
The following domains will be evaluated: bias arising from the randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of the reported result.
An overall risk-of-bias judgment will be assigned for each relevant outcome as low risk, some concerns, or high risk.
Disagreements will be resolved by discussion or consultation with a third reviewer.

Strategy of data synthesis Pairwise random-effects meta-analyses will initially be conducted where clinically and statistically appropriate.
Where a connected evidence network is available, Bayesian random-effects network meta-analysis will be performed to integrate direct and indirect evidence. Individual herbal medicines, natural products, or nutritional supplements will generally be considered separate treatment nodes. Clinically appropriate class-level analyses may be explored separately.
Posterior distributions will be estimated using Markov chain Monte Carlo methods. Relative treatment effects will be reported with 95% credible intervals. Convergence will be evaluated using trace plots, the potential scale reduction factor, and other appropriate diagnostics.
Treatment ranking probabilities and surface under the cumulative ranking curve or equivalent Bayesian ranking measures may be reported, but rankings will be interpreted together with effect estimates, uncertainty, and certainty of evidence.
Statistical heterogeneity will be assessed, and the consistency between direct and indirect evidence will be evaluated using appropriate global and local methods where network geometry permits.
The similarity of background conventional therapy and other potential effect modifiers will be assessed before undertaking network meta-analysis.

Subgroup analysis Where sufficient data are available, subgroup analyses or network meta-regression will explore potential effect modification according to:
- acute versus subacute/chronic OVCF;
- duration since fracture;
- age;
- sex;
- baseline osteoporosis severity or bone mineral density;
- single versus multiple vertebral fractures;
- intervention category, including herbal medicines, natural products, and nutritional supplements;
- treatment duration;
- type of background anti-osteoporosis therapy;
- use of calcium and/or vitamin D as background treatment;
- geographical region; and
- overall risk of bias.

Subgroup analyses will only be undertaken when clinically meaningful and supported by sufficient studies.

Sensitivity analysis Sensitivity analyses will be performed, where sufficient data permit, by:
- excluding studies judged to be at high risk of bias;
- excluding studies with unclear or potentially inadequate randomization;
- excluding very small trials;
- excluding trials with substantial missing outcome data;
- excluding trials in which background conventional treatments differ substantially across treatment arms or studies;
- assessing the influence of alternative prior distributions for heterogeneity parameters.

Where individual preparations have been combined into broader intervention classes, analyses using alternative node definitions will also be explored.

Language restriction No language restrictions will be imposed.

Country(ies) involved Republic of Korea.

Keywords osteoporosis; compression fracture; herbal medicine; natural products; nutritional supplements; adjunctive therapy; Bayesian network meta-analysis.

Contributions of each author
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