INPLASY PROTOCOL

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None declared.

Antiosteoporosis Effect of the Ingredients of Eucommia Ulmoides in Animal Models of Osteoporosis: A Systematic Review and Meta-Analysis

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Review question / Objective: **We presented a systematic review and meta-analysis from the preclinical evidence of Ingredients of Eucommia ulmoidesin in animal models of Osteoporosis to summarize the significant outcomes on efficacy and mechanisms.**
Information sources: **We will search, with no time and No language restrictions, the following databases: PubMed, EMBASE, Web of Science, Cochrane Library, Chinese National Knowledge Infrastructure, Chinese Biomedical Literature Database, and Wanfang Database.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 30 December 2021 and was last updated on 30 December 2021 (registration number INPLASY2021120135).

INTRODUCTION

Review question / Objective: **We presented a systematic review and meta-analysis from the preclinical evidence of Ingredients of Eucommia ulmoidesin in animal models of Osteoporosis to summarize the significant outcomes on efficacy and mechanisms.**

Condition being studied: **Osteoporosis (OP), is a systemic skeletal disease characterized by loss of bone mass and bone microarchitectural deterioration, resulting in increased bone fragility and a greater risk of fractures. Up to now, calcium and vitamin D supplementation are the standard choices for OP treatment. Pharmacological therapies, including**

bisphosphonates, denosumab, and teriparatide, are also recommended to reduce the risk of vertebral or hip fractures in patients with OP. Estrogen therapy, menopausal estrogen plus progestogen therapy, or raloxifene is suitable for postmenopausal women. However, despite the availability of numerous anti-OP medications with diverse pharmacological properties, as well as fixed-dose combination therapy, the targeted therapeutic effect is not attained in significant numbers of individuals with OP, and the mitigation of OP fracture has remained suboptimal. Eucommia ulmoides is the perennial deciduous tree of Eucommia ulmoides Oliv. It is widely sed in the Orthopedics of traditional Chinese Medicine. Now clinically, Eucommia ulmoidesin has not been used to treat OP and there is a lack of clinical evidence, which is the focused pre-clinical question in our study.

METHODS

Search strategy: We will search, with no time and No language restrictions, the following databases : PubMed, EMBASE, Web of Science, Cochrane Library, Chinese National Knowledge Infrastructure, Chinese Biomedical Literature Database, and Wanfang Database. The search string will be built as follows: (Eucommia ulmoid* OR ulmoid* OR Eucommia OR Du-zhong* OR Du zhong) AND (osteoporosis OR osteopenia OR osteoporotic OR "bone loss*" OR "low bone mass" OR "low bone density").

Participant or population: Animal studies.

Intervention: The treatment group received Eucommia ulmoides as monotherapy, regardless of dosage, medicament type, route of administration, and time for the medicine application.

Comparator: Blank treatment or isometric placebo was received in the control group.

Study designs to be included: Only animal studies that assessed the efficacy and safety of Eucommia ulmoides for OP were included, regardless of publication status or language.

Eligibility criteria: We included controlled studies assessing the administration of Eucommia ulmoides for OP animal models established by different methods, regardless of animal species, age, weight, and gender.

Information sources: We will search, with no time and No language restrictions, the following databases : PubMed, EMBASE, Web of Science, Cochrane Library, Chinese National Knowledge Infrastructure, Chinese Biomedical Literature Database, and Wanfang Database.

Main outcome(s): Types of Outcome Measures. The primary outcome measures were the following: (1) bone mineral density (BMD, including BMD-lumbar spine and BMD-femur), (2)serum osteocalcin(S-OCN), (3) bone volume over total volume (BV/TV), (4) trabecular number (Tb.N), (5) trabecular thickness (Tb.Th), (6) trabecular separation (Tb.Sp), (7) bone maximum load, and (8) elasticity modulus.

Additional outcome(s): The secondary outcome measure was the anti-osteoporosis mechanisms of Eucommia ulmoides.

Quality assessment / Risk of bias analysis: Two authors independently performed methodological quality and risk of bias assessment of the included studies using the CAMARADES 10-item quality checklist with minor modification. The modification is listed as follows: D: blinded induction of model (group randomly after modeling), F: use of anesthetic without significant protective and toxic effects on bones, and G: appropriate animal model with complications or risk factors (including age, hyperlipidemia, diabetes, or hypertensive).

Strategy of data synthesis: Risk ratio (RR) for both fixed and random effects models (weighting by inverse of variance) will be used. A continuity correction will

also be used for cells with zero values. Between-study heterogeneity will be assessed using theτ2 2(Cochran Q)and I2 statistics. According to the Cochrane handbook, the 12 will be considered non-important(60%).Results will be assessed using forest plots and presented as RRs for the main outcome and secondary outcomes. An influence analysis will be performed to ascertain the results of the meta-analysis by excluding each of the individual studies. Publication bias will be assessed by a funnel plot for meta-analysis and quantified by the Egger method. Statistical analysis will be conducted using STATA software for Mac v15.0(Stata Corp., College Station, Texas)[module"meta"] and R studio v1.0.136 (The R Foundation for Statistical Computing)[package"meta v4.2"].

Subgroup analysis: We will consider subgroups such as animal species, modeling methods, kind of Eucommia ulmoides, sample size, and dosages of Eucommia ulmoides.

Sensitivity analysis: None reported.

Country(ies) involved: China.

Keywords: Meta-Analysis; Eucommia Ulmoides; Animal Models.

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