INPLASY PROTOCOL

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None declared.

Protective Effect and Possible Mechanisms of Salvia Miltiorrhiza for Diabetic Nephropathy: A Systematic Review and Meta-Analysis of Animal Studies

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Review question / Objective: **The aim of this meta-analysis in animal models is to evaluate the protective effect and possible mechanisms of Salvia miltiorrhiza and its extracts for diabetic nephropathy.**
Information sources: **We will select the studies from nine databases, including the Web of Science, PubMed, Scopus, Cochrane Library, Ovid, China National Knowledge Internet (CNKI), Wanfang Data, VIP Information Chinese Periodical Service Platform (VIP), and Chinese Biomedical Database (SinoMed). The eligible reference will also be included.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 16 August 2022 and was last updated on 01 September 2022 (registration number INPLASY202280060).

INTRODUCTION

Review question / Objective: **The aim of this meta-analysis in animal models is to evaluate the protective effect and possible mechanisms of Salvia miltiorrhiza and its extracts for diabetic nephropathy.**

Condition being studied: **Diabetes is one of the most serious public health problems in the 21st century. Diabetic nephropathy is one of the common chronic complications of diabetes. Epidemiological studies have shown that about 30-40% of DM patients develop nephropathy. Diabetic nephropathy is the main cause of end-stage renal**

disease. At present, the treatment of DN mainly includes strict management of blood glucose and control of blood pressure through renin-angiotensin system blockers, but there are shortcomings in delaying end-stage renal disease. At present, there is an urgent need to find new therapeutic methods to treat diabetic nephropathy. In China, Chinese herbal medicine is widely used to treat diabetic nephropathy. More and more evidences have shown that salvia miltiorrhiza and its extracts may improve diabetic nephropathy by reducing oxidative stress, inhibiting the production of inflammatory mediators, improving hemorheology, regulating glucose and lipid metabolism, and alleviating renal fibrosis. However, the current sample size of in vivo research is small and lacks sufficient evidence. So far, there is no meta-analysis based on preclinical studies to comprehensively explore the protective effect and mechanism of salvia miltiorrhiza and its extracts on diabetic nephropathy. Therefore, through systematic review, this study summarizes the important achievements of salvia miltiorrhiza and its extracts in terms of efficacy and mechanism of action.

METHODS

Search strategy: In this study, two authors will independently search nine electronic databases(Web of Science, PubMed, Scopus, Cochrane Library, Ovid, China National Knowledge Internet (CNKI), Wanfang Data, VIP Information Chinese Periodical Service Platform (VIP), and Chinese Biomedical Database (SinoMed)). To retrieve the research from the database establishment to August 2022. There are no restrictions on the language and year of publication.

Participant or population: Animal models of diabetic nephropathy.

Intervention: Salvia miltiorrhiza or salvia miltiorrhiza extracts.

Comparator: The control group was either treated with a corresponding dose of nonfunctional sterile liquid.

Study designs to be included: Randomized controlled studies.

Eligibility criteria: Included criteria: 1.participants: animal models of diabetic nephropathy, regardless of species, ages or sexes. 2.intervention: salvia miltiorrhiza or salvia miltiorrhiza extracts. The dosage, timing and frequency of the intervention will not be limited. 3.comparison: the control group was either treated with a corresponding dose of nonfunctional sterile liquid. 4.outcomes: the main outcomes should include blood glucose (BG), serum creatinine (Scr), blood urea nitrogen (BUN), 24h urine microalbumin (24h UAlb); 24h urine protein (24h Upro), kidney index (KI) and pathological changes of renal tissue. There must be at least one item to evaluate renal function more comprehensively. The secondary outcomes should include the mechanism of against kidney damage caused by DM. 5. published in a peer-reviewed journal. Excluded criteria: 1.participants: in vitro and human studies; 2.intervention: non monotherapy (combination therapy with other drugs); 3.comparison: the control group was given drug treatment; 4.outcomes: there were no predefined primary outcome measures; 5.study design: cross studies, reviews, meta-analyses, case reports, abstracts; 6.repeated publication.

Information sources: We will select the studies from nine databases, including the Web of Science, PubMed, Scopus, Cochrane Library, Ovid, China National Knowledge Internet (CNKI), Wanfang Data, VIP Information Chinese Periodical Service Platform (VIP), and Chinese Biomedical Database (SinoMed). The eligible reference will also be included.

Main outcome(s): The main outcomes should include blood glucose (BG), serum creatinine (Scr), blood urea nitrogen (BUN), 24h urine microalbumin (24h UAlb); 24h urine protein (24h Upro), kidney index (KI) and pathological changes of renal tissue.

Additional outcome(s): The secondary outcomes should include the mechanism of against kidney damage caused by DM.

Quality assessment / Risk of bias analysis: The Systematic Review Centre for Laboratory Animal Experimentation Risk of Bias toll will be applied to evaluate the risk of bias in individual included studies. Two authors will independently assesse the quality of included studies using the bias risk tool of SYRCLE. The evaluation results are "yes", "no" and "unclear", which respectively represent "low risk of bias", "high risk of bias" and "unclear risk of bias". Any differences will be resolved through consultation with the corresponding authors.

Strategy of data synthesis: All meta analyses will be performed using R software (version 4.1.2). The pooled statistics of the results will be quantitatively determined using the standardized mean difference (SMD) and the corresponding 95% confidence interval (95% CI). We will use I2 and Cochrane's Q test as evaluation indicators. If there is heterogeneity between studies (I2>50% or P<0.1), a random effects model will be used; If not, a fixed effect model will be used.

Subgroup analysis: When the heterogeneity is significant, subgroup analysis shall be carried out according to the method of establishing animal models, dosage of intervention, duration of intervention and type of salvia miltiorrhiza.

Sensitivity analysis: To check the robustness of the main analysis, an omitted sensitivity analysis will be performed, omitting one study at a time.

Country(ies) involved: China.

Keywords: Salvia miltiorrhiza, diabetic nephropathy, animal models, meta-analysis, systematic review.

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