INPLASY PROTOCOL

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Corresponding author:
Xue Xue

xue025004138@163.com

Author Affiliation:
Affiliated Hubei Provincial Hospital of Traditional Chinese Medicine, Hubei University of Chinese Medicine, Wuhan, ChinaCentre for Evidence-Based Chinese Medicine, Beijing University of Chinese Medicine, Beijing, China.

Review Stage at time of this submission: **Preliminary searches.**

Conflicts of interest:
None declared.

Ophiocordyceps sinensis preparation combined with renin-angiotensin system inhibitor for diabetic kidney disease: an umbrella review of systematic reviews and network meta-analysis

Xue, X[4]; Jin, XY[2]; Li, KY[3]; Li, JX[4]; Ye, XL[5]; Liu, Q[6]; Liu, XH[7]; Lu, CL[8]; Wang, XQ[9]; Zhao, FF[10]; Liu, JP[11].

Review question / Objective: **Types of participants: All participants meet diagnostic criteria for diabetic nephropathy (DKD). None of the participants enter renal replacement therapies (including peritoneal dialysis, hemodialysis and kidney transplant). There are no restrictions on age, sex, race, stage of disease, or source of cases.**
Types of intervention: In addition to basic treatment (BT), any ophiocordyceps sinensis preparation added were included in experimental group. BT referred to exercise, nutrition, smoking cessation, glycemic control, blood pressure control, lipid management, and renin-angiotensin system inhibitor (RASi) use. While control group involved "BT alone" or "BT plus placebo" or "BT plus different ophiocordyceps sinensis preparation". No restriction on form or dosage of ophiocordyceps sinensis preparation.
Types of outcome measures: Critical outcomes included: (1) end-point event; (2) albuminuria progression; (3) major adverse cardiovascular and cerebrovascular events (MACCEs).
Important but not critical outcomes involved urine protein testing, renal function testing and adverse events. The specific outcomes on urine protein included 24 hours urinary total protein (24h UTP); urinary albumin excretion rate (UAER); and urinary albumin/creatinine ratio (UACR). The specific outcomes on renal function included serum creatinine (Scr); serum urea nitrogen (SUN); and estimated glomerular filtration rate (eGFR).
Other outcomes were fasting plasma glucose (FPG); glycated hemoglobin A1c (HbA1c); and Syndrome scores.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 15 May 2023 and was last updated on 15 May 2023 (registration number INPLASY202350066).

INTRODUCTION

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dialysis, hemodialysis and kidney transplant). There are no restrictions on age, sex, race, stage of disease, or source of cases.

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Condition being studied: The increasing prevalence of diabetic kidney disease (DKD) rise sharply, and is the leading cause of chronic kidney disease all over the world. Because of high morbidity, high mortality, and high medical costs, DKD has become a global public problem with a significant disease burden.

At present, current treatments for DKD are mainly based on the prevention and control of its risk factors. Previously only RASi with multidisciplinary treatments is effective for DKD. In recent years, some new drugs have been found to be beneficial for DKD patients, such as: sodium glucose cotransporter 2 (SGLT2) inhibitor, and glucagon-like peptide-1 (GLP-1) receptor agonists, etc. But they still have limitations in clinical practice. The progression of DKD has not been completely controlled yet.

Based on traditional Chinese medicine theory, ophiocordyceps sinensis is beneficial for DKD. Previous literature on ophiocordyceps sinensis preparations combined with RASi for DKD has been accumulating, but there was a lack of summary of the overall evidence and comparison between different ophiocordyceps sinensis preparations. Given this, we plan to evaluate the methodological quality of existing SRs, and compare the effectiveness and safety of different ophiocordyceps sinensis preparations to provide objective evidence-based evidence for clinical use.

METHODS

Participant or population: All participants meet diagnostic criteria for diabetic nephropathy (DKD). None of the participants enter renal replacement therapies (including peritoneal dialysis, hemodialysis and kidney transplant). There are no restrictions on age, sex, race, stage of disease, or source of cases.

Intervention: In addition to BT, any ophiocordyceps sinensis preparation added were included in experimental group. BT referred toexercise, nutrition, smoking cessation, glycemic control, blood pressure control, lipid management, and RASi use.

Comparator: Control group involved "BT alone" or "BT plus placebo" or "BT plus different ophiocordyceps sinensis preparation". No restriction on form or dosage of ophiocordyceps sinensis preparation.

Study designs to be included: SRs and/or meta-analyses based on randomized controlled trials (RCTs) were included.

Eligibility criteria: (1) All participants meet diagnostic criteria for diabetic nephropathy (DKD). (2) None of the participants enter renal replacement therapies.(3) SRs and/or meta-analyses based on randomized

controlled trials (RCTs). (4) The application of RASi must be included in the basic treatment.(5) At least one outcome measure as following was reported: renal end-point event; kidney disease progression; MACCEs; 24h UTP; UAER; UACR; Scr; SUN; eGFR; adverse events; FPG; HbA1c; and syndrome scores.

Information sources: We will search the following Chinese and English databases from their inception to May 2023. Chinese databases include China National Knowledge Infrastructure (CNKI), Wan Fang, Chinese Science and Technology Journal Database (VIP), and SinoMed Database. English databases include PubMed, EMBASE, the Cochrane Library, and Web of Science. Two international platforms of registered SR and meta-analysis protocols including INPLASY and PROSPERO will be searched. No language or publication type is imposed.

Main outcome(s): Critical outcomes included: (1) end-point event; (2) albuminuria progression; (3) major adverse cardiovascular and cerebrovascular events (MACCEs).
Important but not critical outcomes involved urine protein testing, renal function testing and adverse events. The specific outcomes on urine protein included 24 hours urinary total protein (24h UTP); urinary albumin excretion rate (UAER); and urinary albumin/creatinine ratio (UACR). The specific outcomes on renal function included serum creatinine (Scr); serum urea nitrogen (SUN); and estimated glomerular filtration rate (eGFR).
Other outcomes were fasting plasma glucose (FPG); glycated hemoglobin A1c (HbA1c); and Syndrome scores.

Quality assessment / Risk of bias analysis: 1. Quality of methodology for systematic review (SR): AMSTAR 2 tool was applied to appraise the methodological quality of the included SRs by two authors independently. Any disagreements were resolved by discussion with corresponding author. The methodological quality of AMSTAR 2 for SR is divided into 16 entries, among which items 2, 4, 7, 9, 11, 13 and 15 are recommended key items for methodological quality. Overall study quality scores were defined as "high" when there was no or one non-critical weakness, "medium" when there was more than one non-critical weakness, "low" when there was one critical flaw with or without non-critical weaknesses or "critically low" when there was more than one critical flaw with or without non-critical weaknesses.
2.Quality of evidence for main findings: Two reviewers will summarize the quality of evidence for main findings using the "Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach", independently. The quality of evidence for the main findings are graded as GRADE working Group grades of evidence.

Strategy of data synthesis: The results will be reported in text, figures and tables. We will use RevMan5.3, GEMTC project, R-project for analysis. RevMan5.3 is used to analysis the effectiveness and safety of each ophiocordyceps sinensis preparation combined with RASi. Moreover, R-project and GEMTC project will be used to conduct a network meta-analysis of RCTs included in all included SRs. The data will be analyzed by adjusting the indirect comparison approach if closed loops were unavailable, while the mixed treatment comparison approach was performed when one or more closed loops were available.

Subgroup analysis: To reduce clinical heterogeneity, we will conduct subgroups analyses of different interventions. Subgroup analyses are required to analyze the effectiveness and safety of different ophiocordyceps sinensis preparations combined with RASi for DKD.

Sensitivity analysis: If the data is available, we will conduct sensitivity analysis to explore the robustness of results.

Country(ies) involved: China.

Keywords: Ophiocordyceps sinensis; diabetic kidney disease; umbrella review; network meta-analysis.

Contributions of each author:
Author 1 - Xue Xue.
Author 2 - Xin-yan Jin.
Author 3 - Ke-ying Li.
Author 4 - Jia-Xuan Li.
Author 5 - Xing-Lan Ye.
Author 6 - Qiang Liu.
Author 7 - Xue-han Liu.
Author 8 - Chun-li Lu.

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