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Protocol for a Comprehensive Meta-Analysis on the Therapeutic Role of Huangkui Capsules in Diabetic Nephropathy

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ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - Data extraction.

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 6 January 2025 and was last updated on 6 January 2025.

INTRODUCTION

Review question / Objective In patients with diabetic nephropathy (P), what is the effect of Huangkui Capsules (I) compared to standard treatment interventions (C) on renal function indicators, glycemic control, lipid profiles, and inflammatory markers (O) as studied in randomized controlled trials and animal studies (S)?

Rationale The rationale for our study is rooted in the pressing need to address the global health challenge of diabetic nephropathy (DN). DN is a progressive complication of diabetes mellitus, leading to significant morbidity and mortality. Despite the availability of some treatments, there is a continuous demand for more effective therapeutic options that can improve patient outcomes and quality of life.

The Huangkui herb, from which Huangkui Capsules (HKC) are derived, has a long history of use in traditional medicine for managing kidney-related conditions. Recent scientific research has begun to uncover the potential of HKC in treating various kidney diseases, including DN. Encouraging evidence from preliminary studies suggests that HKC may offer therapeutic benefits, making it a promising candidate for further investigation.

The rationale for conducting a comprehensive meta-analysis of both clinical and preclinical evidence on HKC is threefold. Firstly, it aims to systematically synthesize and evaluate the existing body of evidence to provide a clear and comprehensive understanding of the therapeutic role of HKC in nephropathies. This is crucial as it allows for the identification of key research areas and the exploration of the effectiveness and mechanisms of action of HKC, particularly in the context of DN. Secondly, by conducting meta-

analyses of clinical and preclinical evidence, the study can pool data from multiple studies, increasing the statistical power and reliability of the findings. Thirdly, the study aims to contribute to the broader understanding of the mechanisms of action of HKC. By examining both clinical and preclinical evidence, the study can provide insights into the biological pathways and targets that HKC may be influencing. This mechanistic understanding is essential for the development of more targeted and effective treatments, and it can also inform the design of future research studies.

The study's focus on DN is particularly relevant given the significant burden of this disease. DN is a leading cause of end-stage renal disease and is associated with a high risk of cardiovascular complications. The current standard of care for DN often involves the use of renin-angiotensin-aldosterone system (RAAS) inhibitors and glucose-lowering medications, but there is still a need for additional therapies that can further improve renal function and reduce the risk of complications.

In conclusion, the rationale for this study is to provide a comprehensive and evidence-based assessment of the therapeutic potential of Huangkui Capsules in the treatment of diabetic nephropathy. By conducting a systematic review and meta-analysis of both clinical and preclinical evidence, the study aims to contribute to the development of more effective treatment strategies for patients with DN, ultimately improving their health outcomes and quality of life. The findings of this study could have significant implications for clinical practice and future research in the field of nephrology.

Condition being studied Diabetic nephropathy (DN) is a chronic and progressive complication of diabetes mellitus, representing a significant global health challenge with a substantial impact on morbidity and mortality. It is characterized by the gradual deterioration of renal function, often marked by the onset of proteinuria, which is the presence of excess protein in the urine. As DN advances, patients experience a decline in kidney function, as evidenced by elevated levels of serum creatinine (SCR) and blood urea nitrogen (BUN). Poor glycemic control is a primary driver of DN, and maintaining optimal blood sugar levels is crucial for mitigating its progression. Additionally, dyslipidemia, a common comorbidity in diabetes, further exacerbates the renal damage. The management of DN is complex and requires a multifaceted approach, including the use of renin-angiotensin-aldosterone system (RAAS) inhibitors and glucose-lowering medications. Despite these interventions, there remains an unmet need for more effective therapies that can enhance renal function and reduce the risk of complications, making DN an area of intense research interest. The potential of Huangkui Capsules (HKC) as an adjunctive treatment for DN is particularly promising, given the encouraging preliminary evidence of its efficacy in improving renal function indicators, glycemic control, lipid profiles, and inflammatory markers. This study aims to systematically evaluate the therapeutic role of HKC in DN through a comprehensive meta-analysis of both clinical and preclinical evidence, thereby contributing to the development of more effective treatment strategies for patients with this debilitating condition.

METHODS

Search strategy (Huangkui Capsules[Title/Abstract] OR Abelmoschus moschatus[Title/Abstract]) AND (Diabetic Nephropathy[Title/Abstract] OR "Diabetic Kidney Disease"[Title/Abstract]) AND (Randomized Controlled Trial[Publication Type] OR Meta-analysis[Title/Abstract] OR Animal Study[Title/Abstract]).

Participant or population Clinical Studies: The primary participants in the clinical studies included in this review are adults diagnosed with diabetic nephropathy. These individuals are typically aged 18 years and above and have a confirmed diagnosis of diabetes mellitus with evidence of kidney damage, as indicated by the presence of albuminuria, reduced glomerular filtration rate (GFR), or other relevant clinical and laboratory findings.

Animal Models of Diabetic Nephropathy: The animal studies included in the review will involve animal models of diabetic nephropathy. These models are typically created using rodents such as rats or mice, which are induced with diabetes through methods such as high-fat diets, streptozotocin (STZ) injections, or genetic modifications. The animals are then monitored for the development of kidney damage, similar to what is observed in human diabetic nephropathy.

Intervention Huangkui capsules (or Hibiscus abelmoschus extract in animal studies) alone or in combination with other conventional treatment.

Comparator Studies where Huangkui capsules were compared with standard treatments for diabetic nephropathy will be included. Standard treatments may include:

Renin-Angiotensin-Aldosterone System (RAAS) Inhibitors: Such as angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs), which are commonly used to reduce

proteinuria and slow the progression of kidney disease.
Glucose-Lowering Medications: Such as metformin, insulin, or other oral hypoglycemic agents, which are essential for managing blood glucose levels in diabetic patients.
Lipid-Lowering Agents: Such as statins, which are used to manage dyslipidemia, a common comorbidity in diabetic patients and a risk factor for cardiovascular disease.

Study designs to be included Randomized controlled trials and animal studies.

Eligibility criteria Studies that are duplicates of other studies included in the review will be excluded to avoid overestimating the effect size.
Studies that do not report sufficient data to calculate effect sizes or that have unclear or incomplete reporting of methods will be excluded.
Studies that do not report on the outcomes of interest (as defined in the PICOS criteria) will be excluded.

Information sources We searched PubMed, Embase, Web of Science, Cochrane Library, China National Knowledge Infrastructure (CNKI), Wan Fang, and China Biology Medicine disc (CBM) from database inception to October 2024 for published literature.

Main outcome(s) Renal Function: 24-hour Urinary Protein Excretion (24h-UPE): Measured in grams or milligrams. A reduction in 24h-UPE indicates improved kidney function; Serum Creatinine (SCR): Measured in micromoles per liter (μmol/L). A decrease in SCR suggests improved kidney function; Glomerular Filtration Rate (eGFR): Measured in milliliters per minute per 1.73 square meters (mL/min/1.73m^2). An increase in eGFR indicates improved kidney function.
Glycemic Control: Fasting Blood Glucose (FBG): Measured in millimoles per liter (mmol/L). A decrease in FBG indicates better glycemic control; Hemoglobin A1c (HbA1c): Measured as a percentage. A decrease in HbA1c indicates better glycemic control over the past 2-3 months.
Lipid Profiles: Total Cholesterol (TC): Measured in millimoles per liter (mmol/L). A decrease in TC indicates improved lipid profiles; Triglycerides (TG): Measured in millimoles per liter (mmol/L). A decrease in TG indicates improved lipid profiles.
Inflammatory Markers: Tumor Necrosis Factor-alpha (TNF-α): Measured in picograms per milliliter (pg/mL). A decrease in TNF-α indicates reduced inflammation; Interleukin-6 (IL-6): Measured in picograms per milliliter (pg/mL). A decrease in IL-6 indicates reduced inflammation; C-reactive Protein (CRP): Measured in milligrams per liter (mg/L). A decrease in CRP indicates reduced inflammation.

Data management Two reviewers (C.L. and X.C.) independently selected eligible studies and recorded reasons for exclusion. Inclusion criteria were as follows: original articles featuring RCTs or animal studies assessing the impact of HKC (or Hibiscus abelmoschus extract in animal studies) on DN; the control group received proven effective positive control drugs and the intervention group was treated with HKC alone or in combination with the control group's medication; and studies reporting at least one predefined outcome measure, including renal function indicators [24-hour urine protein (24h-UPE), albumin/creatinine ratio (ACR), urinary albumin excretion rates (UAER), serum creatinine (SCR), blood urea nitrogen (BUN), glomerular filtration rate (eGFR), albumin (ALB)], glycemic control [fasting blood glucose (FBG), hemoglobin A1c (HbA1c)], lipid profiles [total cholesterol (TC), triglycerides (TG)], and inflammatory markers [interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), C-reactive protein (CRP), hypersensitive-CRP (hs-CRP)]. Studies with inadequate data for analysis or bias assessment were excluded, as were those with unclear methods for establishing DN animal models in animal studies. The same reviewers extracted data from included studies using a standardized Excel spreadsheet, with disagreements resolved by consensus with a third reviewer (X.C.).

Quality assessment / Risk of bias analysis The risk of bias for each eligible RCTs was independently assessed by two reviewers (S.L and Y.Y.) using the Cochrane Risk of Bias tool (ROB 1.0) for randomized trials. Bias was evaluated across seven domains: random sequence generation, allocation concealment, blinding of participants/researchers, outcome assessor blinding, incomplete outcome data, selective reporting and other bias. Each item was rated as 'high risk', 'low risk' or 'unclear'. Reviewers resolved discrepancies by discussion and, when not possible, with adjudication by a third party. The overall evidence and certainty of evidence were evaluated with the GRADE. The quality of included animal studies was independently assessed by two researchers (T.W. and Y.Y.) using the Systematic Review Center for Laboratory Animal Experimentation (SYRCLE) risk-of-bias tool. Any disagreements arising during the evaluation were resolved through discussion with the third author.

Strategy of data synthesis The meta-analysis will be conducted using STATA software. For continuous variables, the weighted mean

difference (WMD) will be employed, with 95% confidence intervals (CIs) calculated. When studies report outcomes using different scales or measurement units, the standardized mean difference (SMD) will be utilized. Heterogeneity among the results will be assessed. If the combined data exhibit no significant heterogeneity ($P \geq 0.10$, $I^2 \leq 50\%$), a fixed-effects model will be applied. Conversely, when significant heterogeneity is present ($P \leq 0.10$, $I^2 \geq 50\%$), the causes of the significant heterogeneity will first be analyzed and further meta-analysis will be performed using a random-effects model.

Subgroup analysis Subgroup analysis will be used to was used to demonstrated differential efficacy across dosage levels.

Sensitivity analysis Begg's test and Egger's test will be used to assess the presence of publication bias.

Country(ies) involved China.

Keywords Huangkui Capsules; Nephropathies; Diabetic nephropathy; Meta-analysis.

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Author 11 - Shaonan Liu - Shaonan Liu conceived this study and contributed to evidence evaluation.