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Potential Application of Myricetin in Diabetic Nephropathy: A Systematic Review and Meta-Analysis of Preclinical Studies

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ADMINISTRATIVE INFORMATION

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 30 March 2026 and was last updated on 30 March 2026.

INTRODUCTION

Review question / Objective This systematic review aims to assess the efficacy and underlying mechanisms of myricetin and its derivatives in treating diabetic kidney disease (DKD) in animal models.Defined by the PICOS framework:Population (P) : DKD model animals, with no restriction on modeling method; Intervention (I) : Myricetin and its derivatives in the experimental group, regardless of administration route, dosage, or treatment duration; Comparison (C) : Control groups receiving equal amounts of saline, distilled water, vehicle, or no intervention; Outcomes (O) : At least one DKD-related outcome reported, including renal function (primary) and secondary outcomes (glucose metabolism, renal pathology, molecular mechanisms); Study design (S) : Peer-reviewed published animal experimental studies on myricetin and its derivatives for DKD.

Condition being studied Diabetic kidney disease (DKD) is one of the most important microvascular complications of diabetes mellitus (DM). It is a chronic renal injury induced by glucose metabolic disorders, clinically characterized by persistent albuminuria and/or a progressive decline in glomerular filtration rate. Patients with DKD often present with comorbid risk factors such as hypertension, obesity, or dyslipidemia, which can further lead to pathological changes including glomerulosclerosis, mesangial proliferation, and thickening of the glomerular and tubular basement membranes. According to statistics, the global prevalence of DM reached 11.11% in 2024, with the total number of patients exceeding 589 million, among whom approximately 20%–40% progress to DKD. DKD is one of the leading causes of end-stage renal disease (ESRD), accounting for about 30%–50% of ESRD cases worldwide. Once patients enter the ESRD stage, they rely on renal replacement therapies such as dialysis or kidney transplantation to sustain life, which not only imposes a heavy medical burden but also significantly increases the risk of cardiovascular

disease, shortening their life expectancy by approximately 16 years.

Myricetin, chemically known as 3,5,7,3′,4′,5′-hexahydroxyflavone, is a natural flavonol compound widely distributed in various plants such as Myrica rubra, tea, onions, and grapes. Modern pharmacological studies have demonstrated that myricetin exhibits multiple biological activities, including antioxidant, anti-inflammatory, anti-tumor, and antiviral effects. It also regulates blood glucose through multiple pathways such as improving insulin resistance, thereby playing an important role in the prevention and treatment of diabetes mellitus (DM).A growing body of evidence has confirmed the significant value of myricetin and its derivative dihydromyricetin in the intervention of diabetic kidney disease (DKD). Yuan et al. found that myricetin acts as a ROCK1 inhibitor to exert anti-proliferative effects, protecting against DKD-related renal fibrosis ; Xu et al. verified that myricetin can improve renal tubulointerstitial fibrosis in DKD by regulating macrophage polarization; Liu et al. established a streptozotocin (STZ)-induced DKD rat model and demonstrated that dihydromyricetin protects renal function by inhibiting the TGF-β1/Smad signaling pathway and reducing collagen deposition in renal tissue .

Currently, although the number of basic studies on the intervention of DKD with myricetin and its derivatives is increasing, there are substantial differences among studies in terms of animal strains, dosages, intervention durations, and outcome measures, leading to inconsistent results and a lack of systematic quantitative evaluation of their efficacy and safety. Meta-analysis, as an important research method in evidence-based medicine, can quantitatively combine results from similar studies, improve statistical power, reduce bias, and thereby more reliably assess the overall effect of interventions. Therefore, this study intends to conduct a systematic review and meta-analysis of animal experiments on myricetin and its derivatives in the treatment of DKD, quantitatively evaluate their effects on renal function, urinary protein, fibrosis, oxidative stress, and other indicators, integrate existing basic research evidence, and objectively clarify the therapeutic potential of myricetin and its derivatives for DKD, so as to provide a reference for subsequent basic research and clinical translational applications.

METHODS

Search strategy We systematically searched four English databases—PubMed, Web of Science, Embase, and the Cochrane Library—as well as four Chinese databases: China National Knowledge Infrastructure (CNKI), VIP Chinese Journal Database, Wanfang Database, and Sinomed. The search strategy combined Medical Subject Headings (MeSH) terms and free-text terms related to myricetin, dihydromyricetin, and diabetic nephropathy, with no restrictions on publication language or region. Additionally, we manually screened the reference lists of relevant field reviews and included studies to supplement eligible research and avoid omissions.

Participant or population DKD model animals, with no restriction on modeling method.

Intervention Myricetin and its derivatives in the experimental group, regardless of administration route, dosage, or treatment duration.

Comparator Control groups receiving equal amounts of saline, distilled water, vehicle, or no intervention.

Study designs to be included Peer-reviewed published animal experimental studies on myricetin and its derivatives for DKD.

Eligibility criteria Inclusion criteria for this study were formulated in accordance with the PICOS principle, as detailed below:

P (Population): Experimental animal models of diabetic kidney disease (DKD), with no restrictions on modeling methods.

I (Intervention): The experimental group was treated with myricetin and its derivatives, with no limitations on administration route, dosage, or treatment duration.

C (Comparison): The control group received equivalent volumes of normal saline, distilled water, corresponding vehicle, or no intervention.

O (Outcome): Studies reporting at least one outcome indicator related to the pathological mechanism or therapeutic efficacy of DKD, including renal function as the primary outcome, and secondary outcomes such as glucose metabolism, renal pathology, and renal molecular mechanisms.

S (Study design): Published in vivo animal experimental studies on myricetin and its derivatives in the treatment of DKD.

Information sources We systematically searched four English databases—PubMed, Web of Science, Embase, and the Cochrane Library—as well as four Chinese databases: China National Knowledge Infrastructure (CNKI), VIP Chinese Journal Database, Wanfang Database, and Sinomed. The search strategy combined Medical Subject Headings (MeSH) terms and free-text

terms related to myricetin, dihydromyricetin, and diabetic nephropathy, with no restrictions on publication language or region. Additionally, we manually screened the reference lists of relevant field reviews and included studies to supplement eligible research and avoid omissions.

Main outcome(s) Renal function indicators, including 24-hour urinary protein excretion, serum creatinine, blood urea nitrogen, 24-hour urine volume, and creatinine clearance rate.

Additional outcome(s) Secondary outcome measures were classified into the following 3 categories:
① Glucose metabolism indicators: body weight, fasting blood glucose, plasma insulin;
② Pathology-related indicators: kidney-to-body weight ratio, α-SMA, TGF-β1, fibronectin, collagen IV;
③ Renal molecular mechanism indicators: SOD, MDA, Beclin-1.

Data management All retrieved results were exported to NoteExpress software (V4.0.0.9855), with duplicate references removed initially. Title and abstract screening were independently performed by two reviewers, who excluded literatures obviously failing to meet the inclusion criteria. Eligible literanges then underwent full-text evaluation to finally determine the included studies. Discrepancies during screening were resolved by consensus through consultation with a third experienced reviewer.
Data extraction was also conducted independently by two reviewers with cross-verification, followed by collation and summarization upon confirmation of consistency. Extracted content was categorized into qualitative and quantitative information. Qualitative data primarily included basic bibliographic information and experimental design protocols, which were systematically summarized and independently assessed by the two reviewers. Quantitative data focused on outcome-related measurements. For studies reporting multiple time-point data, only data from the final intervention time point were extracted for analysis.Specific extracted items were as follows: (1) First author and year of publication; (2) Species, week-age, and sample size of experimental animals; (3) Modeling method of the diabetic kidney disease (DKD) animal model; (4) Therapeutic dose and intervention duration of myricetin and its derivatives; (5) Administration route of myricetin and its derivatives; (6) Outcome-related data were extracted and classified into primary and secondary outcome measures. Primary outcomes were renal function indices, including 24-hour urinary protein quantification, serum creatinine, blood urea nitrogen, 24-hour urine volume, and creatinine clearance rate. Secondary outcomes were divided into the following three categories: ① Glycometabolic indices: body weight, fasting blood glucose, and plasma insulin; ② Pathological indices: kidney/body weight ratio, α-smooth muscle actin (α-SMA), transforming growth factor-β1 (TGF-β1), fibronectin, and collagen-IV; ③ Renal molecular mechanism-related indices: superoxide dismutase (SOD), malondialdehyde (MDA), and Beclin-1.All data were directly extracted from the original texts or obtained from tables and figures in the literatures using Engauge Digitizer software. All included data were presented as mean ± standard deviation (SD). If outcomes in the original literatures were reported as mean ± standard error of the mean (SEM), the Cochrane-recommended formula ($SD = SEM \times \sqrt{n}$) was applied to convert standard error to standard deviation.

Quality assessment / Risk of bias analysis To objectively assess the quality of included studies and minimize the risk of bias, two reviewers independently evaluated the risk of bias in each study using the 10-item Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) Risk of Bias Tool, developed by the centre for evaluating laboratory animal experiments, and cross-checked the results.The SYRCLE Risk of Bias Tool includes the following items: sequence generation, baseline characteristics, allocation concealment, random housing, blinding of caregivers and investigators, random outcome assessment, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias. Each item was rated as “low risk”, “high risk”, or “unclear risk” based on the study design and reporting details.Any discrepancies during the assessment were resolved through discussion and consultation with a third reviewer until a consensus was reached.

Strategy of data synthesis Statistical analyses were performed using Review Manager (RevMan) version 5.4.1 and STATA 15.1 software. All outcome measures included in this study were continuous variables, with data extracted as mean ± standard deviation ($\bar{x} \pm s$).Pooled effect sizes were presented as standardized mean differences (SMD) with corresponding 95% confidence intervals (CI). Given the heterogeneity across included studies in terms of interventions, dosages, intervention durations, and animal

models, a random-effects model was pre-specified for statistical analysis.

Subgroup analysis To explore potential sources of heterogeneity across studies, subgroup analyses were performed in this study based on three dimensions: modeling method, intervention duration, and intervention dosage.

Sensitivity analysis Funnel plot visualization combined with Begg's and Egger's tests was employed to assess publication bias, along with supplementary sensitivity analysis. However, bias analysis was not performed for outcomes with fewer than 10 included studies.

Language restriction No language restriction.

Country(ies) involved China.

Keywords Myricetin;Diabetic Nephropathy;Animal Model;Systematic Review;Meta-Analysis; Preclinical Research.

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