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Rutin for Diabetic Nephropathy: A Systematic Review and Meta-analysis of Preclinical Animal Studies

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ADMINISTRATIVE INFORMATION

Support - This study received no specific grant from any funding agency.

Review Stage at time of this submission - The review has not yet started.

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 26 November 2025 and was last updated on 26 November 2025.

INTRODUCTION

Review question / Objective To systematically evaluate the renoprotective effects of rutin in animal models of diabetic nephropathy and to quantify its impact on renal function, pathological changes, oxidative stress, inflammation, and fibrosis.

Condition being studied Diabetic nephropathy (DN) is one of the most common microvascular complications of diabetes and a major cause of end-stage renal disease. It is characterized by persistent albuminuria, elevation of serum creatinine and urea nitrogen, glomerular hypertrophy, mesangial expansion, and progressive renal fibrosis.
Animal models of DN, such as streptozotocin-induced diabetes, alloxan-induced diabetes, and high-fat diet combined with STZ models, are widely used to mimic the pathological and functional changes observed in human diabetic kidney disease.

This review focuses on evaluating the renoprotective effects of rutin, a natural flavonoid with antioxidant and anti-inflammatory activities, on these experimental models of diabetic nephropathy.

METHODS

Participant or population This review will include in vivo animal models of diabetic nephropathy. Eligible models include streptozotocin-induced diabetes, alloxan-induced diabetes, high-fat diet combined with STZ models, or other validated diabetic nephropathy models in rats or mice.
No restrictions will be placed on species, strain, sex, age, or duration of diabetes.
Studies must include a diabetic group and a diabetic + rutin treatment group to be eligible.

Intervention The intervention of interest is rutin administered alone at any dosage, duration, or route, including oral gavage, intraperitoneal injection, or other methods.

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Studies combining rutin with other compounds will be excluded unless data for rutin alone can be separately extracted.

Comparator The comparator will be untreated diabetic animals or diabetic animals receiving vehicle only. Healthy normal controls may be reported but will not be used as the primary comparison group for effect estimation.

Study designs to be included Controlled in vivo animal studies evaluating the effects of rutin on experimentally induced diabetic nephropathy will be included. Eligible designs include randomized controlled animal studies, non-randomized controlled studies, and studies with parallel group designs that compare diabetic animals receiving rutin versus diabetic controls. In vitro studies, human clinical studies, case reports, reviews, and studies without a control group will be excluded.

Eligibility criteria
Inclusion criteria

In vivo animal studies using validated models of diabetic nephropathy (e.g., STZ-induced diabetes, alloxan-induced diabetes, or high-fat diet + STZ models).

Studies evaluating rutin as a single active intervention.

Presence of a diabetic control group without rutin treatment.

Reporting at least one renal functional, histological, biochemical, or molecular outcome.

Controlled experimental design with extractable data (mean, SD/SEM, and sample size).

Exclusion criteria

In vitro studies, clinical studies, reviews, editorials, or conference abstracts without original data.

Studies using combined therapies where the effect of rutin cannot be isolated.

Studies without a diabetic control group.

Unrelated disease models (non-diabetic kidney injury or other diabetic complications without renal outcomes).

Duplicate publications or incomplete data that cannot be obtained.

Information sources The following electronic databases will be searched: PubMed, Embase, Web of Science, Scopus, CNKI, WanFang Data, VIP, and SinoMed. No date or language restrictions will be applied.
Grey literature will be identified through Google Scholar and ProQuest Dissertations if relevant.
Reference lists of all included articles will be screened manually to identify additional eligible studies.
When necessary, corresponding authors may be contacted to obtain missing or unclear data.

Main outcome(s) Primary outcomes include renal functional parameters related to diabetic nephropathy:

Serum creatinine (Scr)

Blood urea nitrogen (BUN)

24-hour urinary protein or urinary albumin excretion

Effect measures: Continuous outcomes will be synthesized using weighted mean difference (WMD) or standardized mean difference (SMD).

Quality assessment / Risk of bias analysis The risk of bias of included animal studies will be assessed using the SYRCLE's Risk of Bias tool, which is adapted from the Cochrane RoB tool for animal experimentation. The following domains will be evaluated:

Selection bias:

Random sequence generation

Allocation concealment

Performance bias:

Random housing

Blinding of investigators/caregivers

Detection bias:

Blinding of outcome assessors

Attrition bias:

Incomplete outcome data

Reporting bias:

Selective outcome reporting

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Other biases:

Baseline characteristics, inappropriate statistical methods, conflicts of interest

Two reviewers will independently assess the risk of bias, and disagreements will be resolved by a third reviewer. Results will be presented in tabular and graphical formats.

Strategy of data synthesis A meta-analysis will be conducted when at least two studies report the same outcome. Continuous data will be pooled using Weighted Mean Difference (WMD) when outcomes share the same measurement units, or Standardized Mean Difference (SMD, Hedges g) when units differ. A random-effects model (DerSimonian–Laird method) will be applied due to expected heterogeneity in animal models, doses, and study designs.

Heterogeneity will be assessed using the I^2 statistic and χ^2 test. When substantial heterogeneity exists ($I^2 > 50\%$), further exploration through subgroup analysis and sensitivity analysis will be performed.

Forest plots will be generated using RevMan, Stata, or R (meta or metafor package). If ≥10 studies are included for an outcome, publication bias will be evaluated using funnel plots and Egger's regression test.

Subgroup analysis The following subgroup analyses will be performed when data permit:

Animal species: rat vs. mouse

Model type: STZ-induced vs. alloxan-induced vs. diet + STZ models

Rutin dose: low, medium, high doses (as defined by included studies)

Duration of treatment: short-term vs. long-term

Route of administration: oral vs. intraperitoneal

Study quality: low risk vs. unclear/high risk of bias

Subgroup results will help explore sources of heterogeneity and assess the robustness of findings.

Sensitivity analysis Sensitivity analyses will be conducted to evaluate the robustness of the results by:

Excluding studies with high risk of bias

Removing one study at a time (leave-one-out analysis)

Excluding studies with incomplete or imputed data

Comparing fixed-effects versus random-effects models

These analyses will identify influential studies and assess the stability of the pooled effects.

Country(ies) involved China.

Keywords rutin; diabetic nephropathy; diabetic kidney disease; animal models; oxidative stress; inflammation; renal fibrosis; preclinical study.

Contributions of each author

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