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REVIEW

Gene–pathway–organ perspective on quercetin in diabetic complications: A narrative review of preclinical evidence

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Abstract: Diabetic complications involve multiple mechanisms, including metabolic disorders, oxidative stress, inflammation, fibrosis and apoptosis. Quercetin possesses multi-target regulatory potential, but relevant preclinical evidence remains scattered across different organs and signaling pathways. This narrative review aims to synthesize rodent evidence on quercetin-related genes, signaling pathways and organ protection in diabetic complications from a gene–pathway–organ perspective. Relevant rodent studies published from inception to June 2025 were searched in PubMed, EMBASE, Web of Science, Cochrane Library and Springer Link databases. Seventy-eight studies were included after screening. Due to significant heterogeneity among studies, a narrative approach was used for evidence synthesis. Quercetin mainly regulates pathways such as AMPK, PI3K/Akt, Nrf2/HO-1, NF-κB, TGF-β/Smad3, SIRT1 and NLRP3 and is involved in metabolic, cardiovascular, hepatic, renal, nervous, intestinal, wound-healing, reproductive and retinal systems. Evidence is strong in the metabolic-cardiovascular, hepatic and renal systems, moderate in the nervous and intestinal systems and limited in other systems. Current animal evidence suggests that quercetin may act as a multi-target regulator in the intervention of diabetic complications. This "gene-pathway-organ" framework can serve as a hypothesis-generating tool to identify key molecular hubs, compare the strength of evidence across different organs and guide subsequent mechanism validation and translational research.

Keywords: Diabetes mellitus; Diabetic complications; Narrative review; Quercetin; Signaling pathways

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INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia. Even though the management is still centered on glycemic control, the greatest clinical burden of diabetes is the long-term complications of the disease that affect the kidney, the retina, the peripheral and central nervous system, the cardiovascular system, the liver, the skin, the musculoskeletal tissues, the reproductive system and the gastrointestinal tract (Armstrong *et al*., 2023; Harris, 2023; Abbasi, 2024; Farhadi *et al*., 2024; Liu *et al*., 2025). In many cases, these complications coexist; they are insidious, they progress and they account for a major proportion of the diabetes-related disabilities and deaths (Crane *et al*., 2024, Ruder, 2024).

The pathobiology of diabetic complications is multi-layered, involving chronic inflammation, oxidative stress, mitochondrial dysfunction, endoplasmic reticulum stress, apoptosis, fibrosis, ferroptosis, barrier dysfunction and metabolic signaling dysregulation (Elajaili *et al*., 2025; Harithpriya *et al*., 2024; Ramesh *et al*., 2022; Vijayalalitha *et al*., 2023). Because these processes interact across tissues, single-target intervention strategies typically offer only partial protection. This complexity increases interest

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in natural compounds with pleiotropic pharmacological activities.

Quercetin is a naturally occurring flavonoid found in fruits, vegetables and tea (Hou *et al*., 2025; Farhadi *et al*., 2024). Experimental studies showed that quercetin had antioxidant, anti-inflammatory, anti-apoptotic, anti-fibrotic, insulin-sensitizing and angiogenic protective effects (Farhadi *et al*., 2024; Khater *et al*., 2024; Feng *et al*., 2023; Sen *et al*., 2025; Rather *et al*., 2025). In diabetes models, reported mechanisms repeatedly involved adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK), phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt), nuclear factor (erythrocyte-derived 2)-associated factor 2/heme oxygenase 1 (Nrf2/HO-1), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), transforming growth factor β/SMAD3 (TGF-β/Smad3), silencing information regulator 1 (SIRT1) and NOD-like receptor family pyrin domain-containing protein 3 (NLRP3)-related signaling pathways (Abdou *et al*., 2022; Eraky *et al*., 2022; Gaber *et al*., 2025; Zaman and Amin, 2025). However, most existing literature remains fragmented, with most reports focusing on only one organ system or pathway at a time.

The existing reviews have extensively explored the role of quercetin in diabetes, metabolic syndrome, oxidative stress, inflammation and some diabetic complications (Farhadi *et al*., 2024; Liu *et al*., 2025; Chen *et al*., 2025). However, most of these reviews either summarize the pharmacological effects of quercetin in a general way or focus solely on a single organ system, such as the kidneys, cardiovascular system, nervous system, liver, or wound healing (Chen *et al*., 2025; Liu *et al*., 2025; Farhadi *et al*., 2024). Therefore, these reviews fail to clearly compare how the same molecular node recurs across different diabetic complications, nor do they clearly indicate which organ-level conclusions have sufficient, repeated evidence support and which are still at the preliminary stage. The specific conceptual gap addressed here is not the discovery of new molecular networks, but the synthesis of preclinical evidence from a gene–pathway–organ perspective to compare shared mechanisms, evidence density and translational uncertainties across different organs. The gene–pathway–organ perspective is intended as a structured explanatory map, rather than a computationally verified model.

Review approach and scope

The literature was synthesized narratively in a structured manner and was not treated as a systematic review or meta-analysis. Several databases were searched, including PubMed, EMBASE, Web of Science, the Cochrane Library and SpringerLink. The goal was to identify rodent studies on quercetin in diabetes, hyperglycemia and related molecular pathways from database inception to June 2025. To ensure a complete literature search, the following terms were used: ("quercetin" OR "Dikvertin" OR "3,3',4',5,7-Pentahydroxyflavone") and ("diabetes" OR "Diabetes Insipidus" OR "Diet, Diabetic" OR "Prediabetic State" OR "Scleredema Adultorum" OR "Glycation End Products, Advanced" OR "Glucose Intolerance" OR "Gastroparesis")OR ("hyperglycemia" OR "Hyperglycemias" OR "Hyperglycemia, Postprandial" OR "Hyperglycemias, Postprandial" OR "Postprandial Hyperglycemias" OR "Postprandial Hyperglycemia") and ("gene" OR "Gene" OR "Cistron" OR "Cistrons" OR "Genetic Materials" OR "Genetic Material" OR "Material, Genetic" OR "Materials, Genetic") as the search terms. "MeSH Terms", "Keyword Words" and "Free words" were combined in the search strategy (shown in appendix 1). Initially, 1,444 records were found. After the removal of duplicated records and the application of inclusion/exclusion criteria, 78 rodent studies were considered relevant and included in this analysis, as shown in fig. 1. PRISMA-style process information was used only to document the screening process and the number of studies; it should not be interpreted as a statement of quantitative synthesis, risk of bias grading, or meta-analysis certainty provided by the review process.

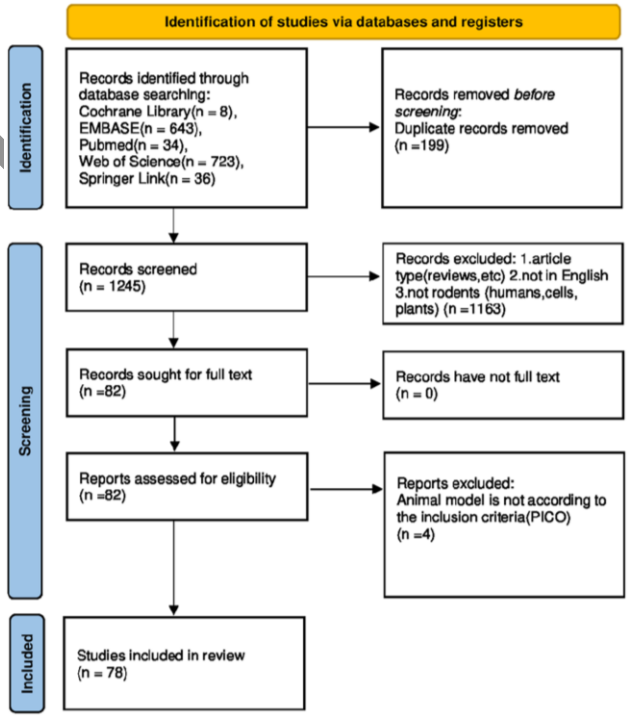


Fig. 1: Flow diagram of literature screening and study selection. A total of 1,444 records were identified from five databases (Cochrane Library, EMBASE, PubMed, Web of Science and Springer Link). After removing 199 duplicates, 1,245 records were screened. Based on inclusion/exclusion criteria (e.g., non-rodent models, non-English articles (n = 0), review articles), 1,163 records were excluded. Full-text assessment was conducted on 82 articles, of which 4 were excluded due to incompatible animal models. A total of 78 eligible animal studies were

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included in this narrative review. This diagram summarizes the literature screening process only and does not indicate that the article was conducted as a PRISMA 2020-compliant systematic review.

This narrative review was revised with reference to SANRA, including clarification of the review's importance and aims, description of the literature search, appropriate referencing, scientific reasoning and presentation of relevant endpoint data (Baethge *et al.*, 2019). It should be distinguished from a systematic review because no formal PRISMA 2020 checklist, protocol registration, risk-of-bias grading, certainty-of-evidence assessment, or meta-analysis was performed. The flow diagram was retained only to transparently document record identification, duplicate removal, screening, full-text assessment and final inclusion; it should not be interpreted as indicating that this narrative review was conducted as a PRISMA 2020-compliant systematic review.

The main evidence pool focused on *in vivo* rodent studies of diabetes or diabetic complications, reporting mechanistic endpoints, including gene expression, protein abundance, phosphorylation and pathway activity, as well as organ-level functional and histological outcomes. Human studies, *in-vitro*-only studies, review articles and reports lacking clear mechanistic evidence were excluded from the main evidence pool. Studies using combination therapies, complex formulations, or quercetin-loaded delivery systems were retained only when relevant to the topic, but should be interpreted with caution, as the specific role of quercetin may not always be isolated.

Because the literature is highly heterogeneous in model type, dosage, route of administration, formulation, duration of treatment, comparator structure and outcome definition, the evidence was considered unsuitable for quantitative pooling. Instead, findings were extracted and grouped into four linked levels: (1) study context, including animal species or strain, diabetes model, organ system, quercetin regimen and comparator; (2) molecular readout, including whether the finding involved mRNA expression, protein abundance, phosphorylation/activity, or downstream functional markers; (3) pathway category, such as AMPK, PI3K/Akt, Nrf2/HO-1, NF-kB/NLRP3, TGF-beta/Smad3, SIRT1, or Bcl-2/Bax-related signaling; and (4) organ-level outcome. Interpretation also considered whether several independent studies reported a mechanism, whether the evidence came from a single model or multiple models, whether the effects were supported by both molecular and functional outcomes and whether combination-treatment designs introduced confounding. These considerations were used qualitatively to classify conclusions as relatively consistent, emerging, or limited, rather than as definitive proof of causality.

Narrative synthesis of the preclinical evidence (Supplementary Tables 1-10)(fig. 2)

Overview of the gene–pathway–organ framework

The reviewed literature supported a recurring pattern in which quercetin was reported to regulate overlapping signaling hubs in several diabetic complications, but the strength of evidence differs substantially by pathway and organ system. The most consistently replicated clusters involve AMPK and PI3K/Akt for metabolic regulation (Park *et al*., 2022; Yoon *et al*., 2025), Nrf2/HO-1 for redox defense (Feng *et al*., 2023; Liu *et al*., 2024), NF-κB and NLRP3 for inflammatory signalling (Hu *et al*., 2020; Zhao *et al*., 2021), TGF-β/Smad3 for fibrotic remodelling (Shakerian *et al*., 2022; Afarin *et al*., 2024; Banerjee *et al*., 2025) and B-cell lymphoma 2/Bcl-2-related X protein (Bcl-2/Bax)-related mechanisms for cell survival and apoptosis (Wang *et al*., 2021; Khajehlandi and Bolboli, 2025) . These pathways should not be read as equally proven across all organs. Evidence is stronger when the same pathway is reported in multiple independent rodent studies, when both molecular and organ-level outcomes move in a coherent direction and when findings are observed across more than one diabetic model. In contrast, pathways reported in only a small number of studies, in a single organ, or in complex co-treatment designs are treated here as emerging or hypothesis-generating.

Therefore, the proposed "gene-pathway-organ" framework is best understood as a conceptual atlas rather than a validated network model. In practical terms, the linkage was constructed by first identifying the reported gene or protein-level change, then assigning that change to a recognized signaling pathway and finally mapping the pathway to the organ system in which the outcome was observed.

Tables 1 and 2 illustrate this logic by showing which organ systems have stronger evidence and which mechanistic hubs recur across organs. Such organization does not prove a direct causal hierarchy, but it clarifies how individual findings are incorporated into the gene–pathway–organ map and where the interpretation still relies on limited or imbalanced evidence.

Organ-system evidence landscape

The evidence is unevenly distributed. The most abundant literature concerns metabolic, pancreatic, cardiovascular, liver and kidney complications, while evidence supporting nervous and gut-related mechanisms is relatively strong. However, evidence regarding the retina, diabetic pregnancy, wound healing, the male reproductive system and the musculoskeletal system is relatively limited. This uneven distribution is significant because it directly affects the reliability of interpreting literature across different systems. Therefore, table 1 separates evidence density from interpretative confidence levels, rather than treating each organ system as equally supported.

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Table 1: Evidence landscape by organ system and interpretive confidence (Farhadi *et al*., 2024; Liu *et al*., 2025; Chen *et al*., 2025).

Organ system / domain	Approximate evidence density	Recurring mechanisms or signals	Interpretive confidence	Main translational note
Metabolic, pancreatic, cardiovascular	High	AMPK, PI3K/Akt, GLUT4, Nrf2/HO-1, NF-κB, eNOS, Bcl-2/Bax	Moderate	Strongest mechanistic clustering, but dosing and model heterogeneity remain substantial
Hepatic	High	Nrf2/HO-1, NF-κB, TXNIP/NLRP3, TGF-β/Smad3, IRS-1/PI3K, PPARα	Moderate	Good mechanistic depth, but outcomes are still preclinical surrogate markers
Renal	High	Nrf2/HO-1, inflammatory cytokines, barrier proteins, TGF-β/Smad3, ferroptosis markers	Moderate	One of the strongest translationally relevant domains, though standardization is limited
Nervous system / cognition	Moderate	P2X4/ p38 mitogen-activated protein kinase (MAPK), Toll-like receptor 4 (TLR4)/ myeloid differentiation primary response 88 (MyD88)/NF-κB, Nrf2, SIRT1/PGC-1α/AMPK, NLRP3	Low to moderate	Mechanistically coherent but based on fewer studies and mixed outcome panels
Gut / intestinal barrier	Moderate	Nrf2-related antioxidant signaling, inflammatory mediators, SGLT1/GLUT5, microbiota shifts	Low to moderate	Promising for cross-organ signaling hypotheses, especially gut–metabolic and gut–retina axes
Wound healing	Limited	TLR4/MyD88/NF-κB, macrophage polarization, angiogenesis-related repair signals	Low	Potentially useful domain, but evidence is sparse and model-specific
Musculoskeletal	Limited	NADPH oxidase (NOX)/ reactive oxygen species (ROS), Nrf2-related antioxidant defense, inflammatory mediators, GLUT4-related insulin sensitivity	Low	Some positive signals, but evidence is uneven and partly formulation-dependent
Male reproduction / diabetic pregnancy	Limited	Oxidative stress markers, steroidogenic genes, HPG-axis signaling, apoptosis-related markers	Low	Interesting endocrine and reproductive signals, but evidence base remains small
Retina	Very limited	Nrf2-related antioxidant defense, gut–retina signaling hypothesis	Very low	Currently hypothesis-generating only

Metabolic, pancreatic and cardiovascular complications

The greatest concentration of evidence was in metabolic and cardiometabolic diseases (39 articles). Quercetin was repeatedly reported to be associated with improved glycemic control, reduced insulin resistance index, improved glucose transport and reduced adipose or hepatic lipid dysregulation (Khater *et al*., 2024; Aranaz *et al*., 2020; Sannappa Gowda *et al*., 2024; de Oliveira Silva *et al*., 2025; Krskova *et al*., 2025). Mechanistically, many studies have linked these effects to AMPK activation, PI3K/Akt signaling, glucose transporter type 4 (GLUT4) regulation, inhibition of sterol regulatory element binding protein-1c (SREBP-1c) and fatty acid synthase (FAS) and regulation of peroxisome proliferator-activated receptor-α (PPARα)-related pathways (Khajehlandi and Bolboli, 2025; Dini *et al*., 2021; Abdou *et al*., 2022; Nasrollahi *et al*., 2022; Snyder *et al*., 2016). Pancreatic protection is also associated with reduced oxidative stress, lowered inflammatory mediators, alleviation of endoplasmic reticulum stress and protection of β-cell function or the expression of regenerative markers (Khater *et al*., 2024; Wang *et al*., 2021).

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Table 2: Recurring mechanistic hubs across organ systems (Farhadi *et al*., 2024; Liu *et al*., 2025; Song *et al*., 2026; Sandilya *et al*., 2026).

Mechanistic hub	Representative genes / proteins	Organ systems in which repeatedly reported	Typical functional implications
Metabolic regulation	AMPK, PI3K/Akt, GLUT4, IRS-1, PPARα, SREBP-1c, FAS	Metabolic, pancreatic, hepatic, cardiovascular, musculoskeletal	Improved insulin sensitivity, glucose utilization, lipid handling and energy balance
Redox defense	Nrf2, HO-1, SOD, CAT, GPX, NOX-related markers	Metabolic, cardiovascular, nervous, hepatic, renal, gut, musculoskeletal, retina	Reduced oxidative stress and improved cellular resilience
Inflammatory control	NF-κB, NLRP3, ASC, IL-1β, TNF-α, TLR4, MyD88	Metabolic, nervous, hepatic, renal, gut, wound-healing	Lower inflammatory signaling and reduced tissue injury
Fibrosis and remodeling	TGF-β/Smad3, α-SMA, collagen-related markers, vimentin, fibronectin	Hepatic, renal, cardiovascular, wound-healing	Attenuation of fibrotic remodeling and structural injury
Cell survival and stress response	Bcl-2, Bax, caspase-related markers, endoplasmic reticulum (ER)-stress mediators, SIRT1/PGC-1α	Pancreatic, cardiovascular, nervous, reproductive	Reduced apoptosis, improved mitochondrial function, stress adaptation
Barrier and vascular function	eNOS, ZO-1, E-cadherin, SGLT1, GLUT5	Cardiovascular, renal, gut	Improved endothelial tone, epithelial integrity and transport regulation

Cardiovascular findings showed a similar pattern. Quercetin was associated with improved endothelial function by increasing endothelial nitric oxide synthase (eNOS) and nitric oxide signaling, reducing oxidative stress through Nrf2/HO-1-related mechanisms and inhibiting inflammation and hypertrophic signaling. Several studies also linked quercetin to anti-apoptotic effects in myocardial tissue, including a favorable shift in the Bcl-2/Bax balance and a weakening of anti-hypertrophic transcriptional pathways (Khajehlandi and Bolboli, 2025; Sannappa Gowda *et al*., 2024; de Oliveira Silva *et al*., 2025; Bartosova *et al*., 2022; Chellian *et al*., 2022).

Nervous-system and cognitive complications

Evidence on diabetic neuropathy and cognitive impairment is limited, but the mechanisms are coherent (a total of 9 articles address this area). Quercetin was associated with alleviating diabetic neuropathic pain by modulating purine receptor P2X4 (P2X4) and MAPK related signaling and involves the anti-inflammatory effects of TLR4, MyD88 and NF-κB. Cognitive findings focused on antioxidant defense, mitochondrial protection, reduced inflammasome activation and improved neuronal survival, repeatedly involving mechanisms related to Nrf2, SIRT1, peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α), AMPK, NLRP3, apoptosis-associated speck-like protein (ASC) and caspase. A small but noteworthy body of literature also suggested a link between gut microbiota remodeling and neurocognitive benefits (Yang *et al*., 2019; Zhao *et al*., 2021; Ebrahimpour *et al*., 2020a; Ebrahimpour *et al*., 2020b; Yang *et al*., 2025; Hu *et al*., 2020; Chamgordani *et al*., 2023; Zhang *et al*., 2025).

Hepatic and renal complications

Liver (9 articles) and kidney (12 articles) complications were among the most supported areas in the reviewed literature. In liver models, quercetin was associated with improved glucose processing, reduced steatosis, decreased inflammatory signaling and reduced fibrotic remodeling. Frequently cited pathways included Nrf2/HO-1, NF-κB, thioredoxin-interacting protein (TXNIP)/NLRP3, TGF-β/Smad3 and insulin signaling nodes such as insulin receptor substrate 1 (IRS-1) and PI3K (Abdou *et al*., 2025; Panchal *et al*., 2012; Gaber *et al*., 2025; Eraky *et al*., 2022).

In kidney models, quercetin was repeatedly associated with reduced oxidative stress, decreased expression of inflammatory cytokines, improved barrier-related proteins such as tight junction protein-1 (ZO-1) and E-cadherin, inhibition of fibrosis markers including α-smooth muscle actin (α-SMA), vimentin, fibronectin and type IV collagen and an emerging antiferroptosis effect involving Nrf2/HO-1, glutathione peroxidase 4 (GPX4) and cysteine/glutamate antitransporter solute carrier family 7 member (SLC7A11). These two systems also illustrated an important cross-organ theme: quercetin was often associated with the simultaneous regulation of metabolic, inflammatory and fibrotic pathways, suggesting that its reported benefits could not be simply reduced to antioxidant activity (Xu *et al*., 2025; Gao *et al*., 2018; Zhao *et al*., 2024; Feng *et al*., 2023).

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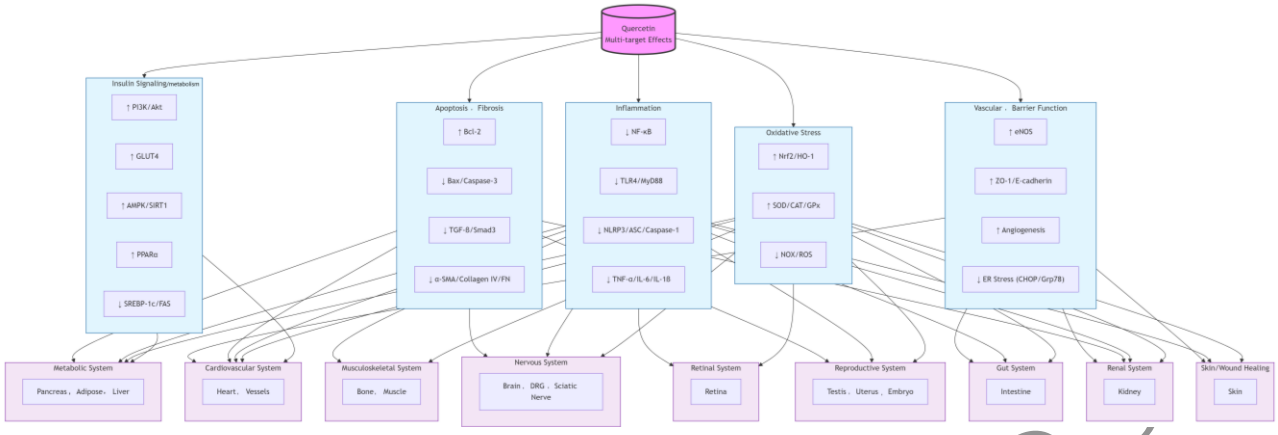


Fig. 2: Schematic representation of the gene–pathway–organ framework for quercetin's action in diabetic complications. The revised high-resolution diagram summarizes the multi-target mechanisms of quercetin across different organ systems. The central column presents five functional modules: insulin signaling/metabolism, apoptosis and fibrosis, inflammation, oxidative stress and vascular/barrier function. Key pathway labels and organ connections have been clarified to improve readability.

Table 3: Priority areas for strengthening the evidence base and translational relevance (Liu *et al*., 2025; Song *et al*., 2026; Sandilya *et al*., 2026).

Priority area	Why it matters	Practical recommendation
Standardized animal models and outcome panels	Current heterogeneity weakens cross-study comparison and inflates narrative uncertainty	Use harmonized model descriptions, dose rationale, treatment duration, and shared outcome sets across major organ systems
Gene-level versus protein-level reporting	Many studies blur expression, abundance, pathway activity, and physiologic effect	Report clearly whether findings reflect mRNA, protein abundance, phosphorylation/activity, or downstream functional readouts
Comparative multi-organ studies	Most evidence comes from single-organ designs, limiting cross-organ interpretation	Design studies that evaluate several organs within the same diabetic model and quercetin regimen
Formulation and pharmacokinetics	Low oral bioavailability remains a major translational barrier	Compare conventional quercetin with optimized formulations using pharmacokinetic and safety endpoints
Negative and conflicting findings	Positive-reporting bias may exaggerate confidence	Encourage full reporting of null, weak, or organ-specific effects to define realistic boundaries of efficacy
Translational linkage to clinical endpoints	Molecular readouts alone cannot establish clinical relevance	Bridge preclinical pathways to outcomes with clearer translational meaning, then test in higher-quality clinical studies

Discoveries related to the gut, wound healing, musculoskeletal system, reproductive system and retina

Research in other organ systems is limited but still informative. In the gut, quercetin was associated with enhanced barrier integrity, reduced inflammatory signaling and reduced glucose transport via sodium-glucose cotransporter 1 (SGLT1) and glucose transporter type 5 (GLUT5)-related mechanisms and was also reported to regulate the microbiome (Liu *et al*., 2024; Bhattacherjee *et al*., 2017). In wound-healing models, quercetin was associated with reduced biofilm load, improved angiogenesis and macrophage polarization from a pro-inflammatory M1 state via TLR4/MyD88/NF-κB signaling. Musculoskeletal evidence suggested antioxidant and anti-inflammatory effects and in some studies, quercetin improved bone regeneration parameters through advanced delivery systems (Mayasa *et al*., 2024; Nain *et al*., 2023; Eraky *et al*., 2022; Fu *et al*., 2020).

Reproductive findings remained preliminary but suggested that quercetin may influence endocrine and steroidogenic signaling, oxidative stress and apoptosis in male diabetic reproductive dysfunction (Mansour *et al*., 2025; Wang *et al*., 2022), while a small body of work in diabetic pregnancy pointed to embryo-protective and anti-stress effects (Bolouki *et al*., 2020a; Bolouki *et al*., 2020b; Cao *et al*., 2016). For the retina, only limited evidence was available in the reviewed literature, but the gut–retina axis and Nrf2-related redox signaling emerged as potentially relevant directions (Liu *et al*., 2024) (Table 2).

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DISCUSSION

What this review adds beyond existing reviews

The literature already contained broad reviews of quercetin in diabetes and metabolic disease. The added value of the present synthesis is narrower and more specific: it focused on diabetic complications rather than diabetes in general, emphasized preclinical mechanistic evidence, compared the maturity of evidence across organ systems and organized the literature by gene–pathway–organ structure. Although the gene–pathway–organ organization does not create a validated systems-biology model, it made the literature easier to compare and exposed recurring hubs that may otherwise remain scattered across organ-specific studies (Farhadi *et al*., 2024; Liu *et al*., 2025).

Recurring mechanistic hubs across organ systems

A cross-organ reading of the literature suggested four recurrent mechanistic clusters, but these clusters differ in evidentiary maturity. First, the metabolic-regulatory cluster centered on AMPK, PI3K/Akt, GLUT4 and lipid-handling genes was among the most consistently reported because it appeared across metabolic, pancreatic, hepatic, cardiovascular and musculoskeletal studies. Second, the redox-defense cluster centered on Nrf2/HO-1, superoxide dismutase (SOD), catalase (CAT) and GPX-related antioxidant machinery was also relatively consistent, although individual studies varied in whether they reported enzyme activity, protein abundance, or transcript-level changes. Third, the inflammatory cluster centered on NF-κB, NLRP3, ASC, interleukin-1β (IL-1β), tumor necrosis factor α (TNF-α) and TLR4/MyD88-related signaling was biologically coherent but not always supported by the same marker panel across studies. Fourth, the remodeling and cell-survival cluster involving TGF-β/Smad3, α-SMA, collagen-related markers and Bcl-2/Bax-associated apoptosis control was important for organ injury. Still, the evidence is more organ-specific and should not be overextended to all diabetic complications. These clusters are therefore used as interpretive anchors rather than as ranked therapeutic targets (Liu *et al*., 2025; Xu *et al*., 2025; Farhadi *et al*., 2024).

Heterogeneity of evidence and methodological limitations

The interpretative value of the preclinical literature is limited by its high heterogeneity

The included studies vary in animal strains, diabetes models, routes and durations of quercetin administration, formulations, control group structures and endpoint definitions. In many areas, only one to five studies report a specific mechanistic target, making robust assessments of consistency difficult. Furthermore, the literature is predominantly positive, with conflicting, neutral, or negative results being less frequently reported. For example, formulation-based or combination therapy studies may show stronger effects than conventional quercetin and metabolic benefits observed in one rodent model may not be reproducible in another model with different diets, strains, or disease durations. Some studies have also reported molecular-level changes, but functional organ endpoints have not improved concurrently. These characteristics do not negate the evidence reviewed but indicate that mechanistic conclusions should be considered convergent signals in the preclinical literature rather than definitive proof of human treatment efficacy (Liu *et al*., 2025; Farhadi *et al*., 2024).

Implications for translation

Pharmacokinetics and formulation development of quercetin remain major obstacles to its clinical translation. Oral absorption is poor, many preclinical studies used high or non-physiological doses and formulation methods vary considerably. Nanoformulations and targeted delivery systems show promise but are still in the research and development stage, requiring more evidence regarding safety, reproducibility, scalability and regulatory acceptance.

Furthermore, molecular benefits observed in mouse studies should not be directly assumed to translate into clinically meaningful effects in humans, such as protecting renal function, slowing the progression of retinopathy, alleviating neuropathic pain, or reducing the incidence of cardiovascular events. These gaps indicate the need to conduct pharmacokinetic studies, standardized formulation development and well-designed translational studies before making claims for clinical application (Liu *et al*., 2025; Chen *et al*., 2025; Farhadi *et al*., 2024).

Future directions

The next investigations should therefore follow a more integrated preclinical strategy, with well-stated justifications for the dosing, clear considerations for the formulation, consistent delivery methods and common outcome measures across the main organ systems. The pragmatic usefulness of the gene-pathway-organ model is that it can guide experimental design: the scientist may choose a particular model of diabetes, apply a given quercetin protocol, measure the same molecular node across different organs and determine whether the pathway is protective in some organs or across many systems. Moreover, the gene–pathway–organ organization helps reviewers and pharmacologists identify mechanisms that require replication, results that are premature for direct clinical use and organ systems that remain insufficiently studied. It also provides a practical strategy for mechanism validation, formulation research and the selection of translational endpoints (Liu *et al*., 2025; Farhadi *et al*., 2024).

Limitations

This review has several limitations

First, the evidence was synthesized narratively rather than through a formal systematic review or meta-analysis.

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Second, the evidence base is heterogeneous and predominantly reports favorable results, raising concerns about publication bias and making direct comparisons between studies harder. Third, for several organ systems, there are only a small number of investigations, so one cannot make very reliable generalizations from these few studies to many organs. Fourth, the source materials show differences among gene expression, protein levels, pathway activation and physiological effects, with inconsistent levels of detail and precision in the source literature. Fifth, progress in clinical application is hampered by problems such as poor oral absorption, inconsistent formulations and differences between rodent models of disease and real human diabetic complications (see Table 3) (Liu *et al.*, 2025; Farhadi *et al.*, 2024). Although a flow diagram was used to summarize the screening process, this review did not include formal protocol registration, PRISMA 2020 checklist reporting, risk-of-bias assessment, certainty grading, or quantitative synthesis.

CONCLUSION

Existing preclinical data suggest that quercetin may act as a multi-target modulator of diabetic complications through metabolic regulation, oxidative stress defense, inflammatory control, anti-fibrotic signaling and cell-survival pathways (Liu *et al*., 2025; Farhadi *et al*., 2024). However, these conclusions should be interpreted cautiously because the supporting studies are heterogeneous and remain largely rodent-based. The main value of the gene-pathway-organ concept is not to establish a definitive mechanistic model, but to organize a dispersed body of work comparably. Its practical value lies in its inspiration and methodology: it can identify frequently involved molecular nodes, identify areas with dense or sparse evidence, highlight areas with contradictions or insufficient research and provide verifiable priority directions for future drug development, formulation research and translational validation.

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Authors' contributions
Jie Zhan: Conceptualization, Validation, Writing – Original Draft, Writing – Review & Editing, Funding Acquisition; Zhixin Chen: Conceptualization, Investigation, Writing – Original Draft, Writing – Review & Editing; Bowen Zhang: Conceptualization, Methodology, Formal Analysis, Writing – Original Draft, Writing – Review & Editing; Xiaojuan Wen: Conceptualization, Methodology, Formal Analysis, Writing – Original Draft, Writing – Review & Editing; Yujing Chen: Conceptualization, Methodology, Formal Analysis, Writing – Original Draft, Writing – Review & Editing; Yanyan Zhu: Conceptualization, Resources, Writing – Original Draft, Writing – Review & Editing; Ming Thong Ong: Conceptualization, Validation, Writing – Review & Editing, Supervision. Fangying Chen: Conceptualization, Validation, Data Curation, Writing – Original Draft, Writing – Review & Editing, Visualization, Project Administration; Xiaohua Chen: Conceptualization, Writing – Review & Editing.

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Data availability statement
All data generated or analyzed during this study are included in this article and its supplementary information files.

Ethical approval
Not applicable.

Consent to publication
The authors confirm that the submitted manuscript is original, has not been published previously and is not under consideration elsewhere.

Conflict of interest
The authors declare that they have no conflict of interest.

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