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Formononetin-mediated renoprotection; explaining the interplay of TGF-β, NF-κB, and Nrf-2 signaling in kidney disease

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ABSTRACT

Kidney diseases, encompassing both acute injury and chronic progression toward fibrosis, are fundamentally driven by intertwined pathways of oxidative stress, chronic inflammation, and aberrant tissue remodeling. Formononetin, a naturally occurring isoflavone, has detected as a potent renoprotective agent capable of interrupting this pathological cascade through coordinated modulation of key signaling networks. At the molecular level, formononetin exerts its therapeutic effects by simultaneously activating the Nrf-2 antioxidant axis while suppressing the pro-inflammatory NF-κB and pro-fibrotic TGF-β pathways. Then, activation of Nrf-2 enhances the transcription of cytoprotective enzymes, effectively neutralizing reactive oxygen species and preserving mitochondrial integrity in renal tubular and glomerular cells. This antioxidant surge reciprocally dampens NF-κB activation, thereby reducing the expression of inflammatory cytokines, chemokines, and adhesion molecules that perpetuate leukocyte infiltration and parenchymal damage. Concurrently, formononetin interferes with TGF-β signaling by attenuating Smad phosphorylation and downstream epithelial-mesenchymal transition, eventually reducing excessive extracellular matrix deposition and fibrotic scarring. The triad of Nrf-2 upregulation, NF-κB inhibition, and TGF-β suppression establishes a synergistic regulatory loop that restores redox homeostasis, mitigates inflammatory amplification, and halts fibrogenesis. Preclinical models consistently demonstrate that formononetin administration improves glomerular filtration, reduces proteinuria, and preserves renal architecture. These mechanistic insights position formononetin as a promising multi-target therapeutic candidate for kidney disease, warranting further translational research to optimize dosing, bioavailability, and clinical applicability in human nephropathies.

Review

Introduction

Formononetin-mediated renoprotection represents an exciting frontier in the pharmacological management of kidney disease, particularly through its modulation of three interconnected signaling pathways of transforming growth factor -β (TGFβ), nuclear factor kappa B (NF-κB) and nuclear factor erythroid 2-related factor 2 (Nrf2) (1). Renal inflammation, oxidative stress, and fibrosis constitute the pathological triad underpinning progressive kidney disorders including diabetic nephropathy, acute

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Implication for health policy/practice/research/medical education:
Kidney disease progression is largely driven by chronic inflammation, oxidative stress, and fibrotic remodeling, processes intricately regulated by the TGF-β, NF-κB, and Nrf-2 signaling pathways. Formononetin, a naturally occurring isoflavone, has detected as a promising renoprotective agent through its capacity to modulate these interconnected pathways. By suppressing TGF-β activation, formononetin attenuates epithelial-mesenchymal transition and extracellular matrix accumulation, thereby mitigating progressive renal fibrosis. Concurrently, it inhibits NF-κB nuclear translocation, reducing pro-inflammatory cytokine release and diminishing persistent inflammatory injury. Importantly, formononetin activates Nrf-2, enhancing the transcription of cytoprotective antioxidant enzymes that neutralize reactive oxygen species and restore cellular redox homeostasis. The coordinated modulation of these cascades reveals a synergistic mechanism wherein formononetin simultaneously dampens profibrotic and inflammatory signaling while reinforcing endogenous antioxidant defenses. This multilayered interplay focuses on formononetin's substantial therapeutic potential in halting kidney disease progression and preserving long-term renal function.
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kidney injury (AKI), and chronic kidney disease, and the global escalation of these conditions demands therapeutic strategies capable of addressing their multifactorial etiology (2). Formononetin, a naturally occurring isoflavone identified as 7-hydroxy-4'-methoxyisoflavone, has found as a promising candidate due to its capacity to employ multiple molecular targets that modulate the above mentioned pathological processes (1). Its renoprotective profile encompasses anti-inflammatory, antioxidant, antifibrotic, and antiapoptotic activities, positioning it as a multifunctional modulator rather than a single-pathway inhibitor, a distinction of considerable therapeutic relevance given the complex crosstalk characterizing renal pathophysiology (3). At the heart of formononetin's mechanism lies its ability to recalibrate the delicate equilibrium between profibrotic, proinflammatory, and pro-oxidant signaling on one hand, and protective, reparative, and homeostatic pathways on the other, with TGFβ, NF-κB, and Nrf2 serving as pivotal nodes in this regulatory network (3). Preliminary studies detected that, TGFβ signaling, particularly through its canonical Smad-dependent pathway, acts as a master regulator of renal fibrosis, driving the transdifferentiation of tubular epithelial cells and fibroblasts into myofibroblasts, stimulating excessive deposition of extracellular matrix components such as collagen I, fibronectin, and α-smooth muscle actin, and lastly directing toward architectural distortion across with functional decline characteristic of end-stage kidney disease (1,4). In diabetic nephropathy and other progressive renal disorders, persistent hyperglycemia, advanced glycation end-products, and hemodynamic stressors converge to amplify TGF-β1 expression and activation, establishing a self-perpetuating cycle of fibrogenesis that proves notoriously resistant to conventional monotherapies (5). Formononetin intervenes in this cascade at multiple pathways; since, mechanistic investigations reveal that it suppresses the expression of TGF-β1 (6). Secondly, formononetin attenuates phosphorylation and nuclear translocation of Smad2/3 (7), and downregulates downstream profibrotic effectors including connective tissue growth factor and plasminogen activator inhibitor-1, thereby disrupting the fibrotic signal propagation (8,9). Notably, formononetin's antifibrotic action is not merely suppressive but appears to involve a rebalancing of TGF-β's dual roles, as this cytokine also possesses context-dependent protective functions in tissue repair and immune regulation, suggesting that formononetin may fine-tune rather than abolish TGF-β signaling to preserve physiological homeostasis while curbing pathological fibrosis (1,10). Parallel to its modulation of fibrotic pathways, formononetin exerts profound anti-inflammatory effects largely mediated through inhibition of NF-κB, a transcription factor complex that serves as a central orchestrator of the renal inflammatory response (3). In the next step, NF-κB activation, triggered by diverse stimuli including cytokines, oxidative stress, and pathogen-associated molecular patterns, promotes the transcription of a vast array of proinflammatory mediators such as interleukin-6, interleukin-1beta, tumor necrosis factor-alpha, monocyte chemoattractant protein-1, and inducible nitric oxide synthase, all of which contribute to leukocyte infiltration, parenchymal damage, and the perpetuation of chronic kidney injury (11,12). Formononetin interrupts this inflammatory cascade by preventing the phosphorylation and degradation of IκBα, the inhibitory protein that sequesters NF-κB in the cytoplasm, thereby blocking nuclear translocation of the p65/p50 heterodimer and subsequent DNA binding to κB-responsive promoter elements (13). This upstream inhibition translates into measurable reductions in circulating and tissue levels of proinflammatory cytokines, diminished expression of adhesion molecules that facilitate immune cell recruitment, and attenuation of inflammatory cell infiltration into renal parenchyma, as demonstrated in experimental models of gentamicin-induced nephrotoxicity, methotrexate-

induced AKI, and diabetic kidney disease (3,14). In this overview, we sought to consider, formononetin-mediated renoprotection, through explaining the interplay of TGFβ, NF-κB, and Nrf2 signaling in kidney disease.

Search strategy

A literature search was conducted using the following electronic databases: PubMed, Google Scholar, DOAJ, Web of Science, EBSCO, Scopus, and Embase. Relevant keywords utilized in the search strategy comprised: chronic kidney disease, Formononetin, transforming growth factor-beta, acute kidney injury, epithelial-mesenchymal transition, fibrosis, inflammation, oxidative stress and antioxidant.

Anti-inflammatory efficiency of formononetin

The anti-inflammatory efficacy of formononetin is further amplified by its capacity to modulate upstream kinases such as p38 mitogen-activated protein kinase and c-Jun N-terminal kinase, which phosphorylate and activate components of the NF-κB pathway, creating a multi-layered inhibitory effect that enhances therapeutic robustness (3,15). Perhaps most intriguingly, formononetin's renoprotective repertoire extends to the augmentation of endogenous antioxidant defenses through activation of the Nrf-2 pathway (14). It should remember that, Nrf-2 pathway is a master regulator of cellular redox homeostasis that coordinates the expression of several cytoprotective genes encoding antioxidant enzymes, phase II detoxifying proteins, and molecules involved in glutathione synthesis and recycling (16,17). Under basal conditions, Nrf-2 is bound to its cytoplasmic inhibitor Keap1 and targeted for proteasomal degradation, but oxidative or electrophilic stress induces conformational changes in Keap1 that liberate Nrf-2, allowing its translocation to the nucleus where it heterodimerizes with small Maf proteins and binds to antioxidant response elements in target gene promoters (14,15,18). Formononetin potentiates this protective role through multiple mechanisms; since, it strengthens Nrf-2 nuclear accumulation, upregulates the expression and activity of heme oxygenase-1, NAD(P)H:quinone oxidoreductase 1, superoxide dismutase, and catalase, and suppresses the generation of reactive oxygen species by inhibiting NADPH oxidase isoforms that serve as major sources of renal oxidative stress (1,3). The activation of Nrf2 by formononetin is not merely an isolated antioxidant effect but appears to be functionally linked to its anti-inflammatory and antifibrotic actions through several layers of molecular crosstalk (1,18). First, Nrf2 activation can directly suppress NF-κB signaling through multiple mechanisms (19). Given that, heme oxygenase-1, as a canonical Nrf2 target generates carbon monoxide and biliverdin (20). Recent studies detected that, both of them possess anti-inflammatory properties and can inhibit IκB (inhibitors-of-kappaB) kinase activity (21). Thereby preventing NF-κB activation creating a reciprocal inhibitory relationship wherein enhancement of one pathway constrains the other (22). Second, Nrf2-mediated reduction of oxidative stress diminishes the activation of redox-sensitive kinases such as transforming growth factor-β-activated kinase 1, which phosphorylates and activates both Smad and NF-κB pathway components, thereby interrupting a key amplification loop that links oxidative injury to fibrosis and inflammation (23). Third, more recent studies suggest that formononetin's activation of Nrf2 may be facilitated by its ability to upregulate sirtuin 1 (SIRT1), as a NAD^+-dependent deacetylase that deacetylates both Nrf2 and NF-κB, enhancing the transcriptional activity of the former while suppressing the latter, thus establishing a SIRT1-dependent axis that coordinately regulates redox balance and inflammatory tone (3,24,25). This SIRT1-Nrf-2-NF-κB axis represents a particularly elegant example of how formononetin's multi-targeting profile enables synergistic modulation of interconnected pathways rather than isolated pathway inhibition (18). The interplay between TGFβ and Nrf2 signaling adds another dimension to formononetin's renoprotective mechanism, as oxidative stress is both a consequence and a driver of TGF-β-mediated fibrogenesis (6,18). Reactive oxygen species can activate latent TGFβ through matrix metalloproteinase-mediated cleavage of its latency-associated peptide, while TGFβ signaling in turn stimulates NADPH oxidase expression and mitochondrial dysfunction, creating a vicious cycle of oxidative stress and fibrosis (26). Following suppressing TGFβ/Smad signaling and activating Nrf2-dependent antioxidant responses, formononetin disrupts this reciprocal amplification, reducing both the generation of profibrotic stimuli and the oxidative milieu that potentiates their effects (3,27). Furthermore, Nrf2 activation has been shown to attenuate epithelial-to-mesenchymal transition, a key cellular process in renal fibrosis that is potently induced by TGFβ, suggesting that formononetin's enhancement of Nrf2 signaling may directly counteract TGFβ-driven phenotypic conversion of renal epithelial cells (1,28). The consequence of formononetin's properties is further illustrated by the observation that formononetin's suppression of renal fibrosis in diabetic models correlates with coordinated down-regulation of TGFβ1, fibronectin, and α-smooth muscle actin alongside upregulation of Nrf2, heme oxygenase-1, and SIRT1, indicating that its antifibrotic efficacy emerges from integrated pathway modulation rather than isolated target engagement (1,6, 18). Beyond these core pathways, formononetin's renoprotective effects are augmented by its influence on additional molecular mediators that intersect with

TGFβ, NF-κB, and Nrf2 signaling (1,3). For instance, formononetin has been shown to inhibit p53 activation, a tumor suppressor protein that, when chronically activated in renal cells under metabolic stress, promotes cellular senescence, apoptosis, and the secretion of profibrotic and proinflammatory factors that exacerbate kidney injury (29). By attenuating p53 signaling, formononetin may preserve renal cell viability and function while reducing the paracrine signals that activate fibroblasts and immune cells (1, 29). Similarly, formononetin's modulation of nicotinamide adenine dinucleotide phosphate oxidase isoforms, particularly NOX4 which is upregulated in diabetic kidneys and contributes to both oxidative stress and TGFβ activation, represents another node of intervention that amplifies its effects on the core triad of pathways (1,30).

Pharmacokinetic profile of formononetin

The pharmacokinetic profile of formononetin, including its bioavailability, tissue distribution, and metabolic stability, also influences its therapeutic potential, and while these parameters continue to be characterized, existing data suggest that formononetin achieves biologically relevant concentrations in renal tissue following oral administration, supporting its translational feasibility (15,27). Importantly, the multi-targeting nature of formononetin may confer advantages over single-agent therapies in complex diseases like chronic kidney disease, where compensatory pathway activation often limits the efficacy of narrowly focused interventions (1,31). By concurrently reducing profibrotic, proinflammatory and pro-oxidant signals while enhancing cytoprotective and homeostatic responses, formononetin may achieve a more comprehensive and durable renoprotective effect. This systems-level modulation is particularly relevant given the dynamic interplay between TGF-β, NF-κB, and Nrf-2 (1,3). Numerous studies demonstrated that, NF-κB-driven inflammation induces TGF-β expression (11). In the next step, TGF-β can amplify oxidative stress through NADPH oxidase upregulation; while oxidative stress can activate both NF-κB and TGF-β signaling; then creating interconnected feedback loops that perpetuate renal injury (32,33). Moreover, formononetin's ability to interrupt multiple nodes within this network may therefore disrupt pathological amplification more effectively than targeting any single pathway in isolation (7,34). Nevertheless, several considerations warrant attention as formononetin advances toward clinical evaluation. First, the dose-dependency and temporal dynamics of its effects on different pathways require further characterization, as excessive suppression of TGF-β or NF-κB could potentially impair physiological tissue repair or immune surveillance (34,35). Furthermore, the potential for formononetin to interact with conventional renoprotective medications, such as angiotensin-converting enzyme inhibitors or sodium-glucose cotransporter-2 inhibitors, merits investigation to identify synergistic combinations or potential antagonisms (14,36). Besides, interindividual variability in formononetin metabolism, influenced by genetic polymorphisms in drug-metabolizing enzymes or gut microbiota composition, may affect therapeutic responses and necessitates personalized dosing strategies (37,38).

Conclusion

Formononetin arises as a promising therapeutic agent in kidney disease by orchestrating a coordinated modulation of TGF-β, NF-κB, and Nrf2 signaling pathways, which collectively govern inflammation, fibrosis, and oxidative stress. In renal pathology, persistent TGF-β activation drives extracellular matrix accumulation and epithelial-mesenchymal transition, whereas NF-κB amplifies inflammatory cascades through sustained cytokine transcription. Formononetin effectively attenuates both pathways, suppressing fibrotic remodeling and dampening leukocyte infiltration. Concurrently, it potently activates Nrf2, a master regulator of cellular antioxidant defense, promoting its nuclear translocation and the subsequent upregulation of cytoprotective enzymes such as heme oxygenase-1 and NQO1 [NAD(P)H: quinone oxidoreductase 1]. This antioxidant response not only neutralizes reactive oxygen species but also exerts reciprocal cross-inhibition on NF-κB and TGF-β signaling, establishing a self-reinforcing protective circuit. The dynamic interplay among these pathways emphasizes formononetin's many-sided mechanism; by blunting pro-fibrotic and pro-inflammatory drivers while amplifying endogenous redox homeostasis. This agent also, effectively interrupts the progressive cascade of renal injury and facilitates structural recovery. Accumulating preclinical data confirm that this tripartite modulation consistently preserves glomerular filtration, minimizes proteinuria, and mitigates histological deterioration. Though clinical validation remains pending, formononetin's capacity to simultaneously target interconnected pathogenic networks positions it as a highly viable candidate for novel renoprotective interventions. Hence, next studies should prioritize pharmacokinetic optimization, target specificity, and translational dosing frameworks to fully realize its therapeutic promise in managing chronic kidney disease.

Authors' contribution

Conceptualization: Xurshida Jurayeva and Mamurakhon Yuldasheva.
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Writing–original draft: All authors.
Writing–review and editing: All authors.

Conflicts of interest

The authors declare that they have no competing interests.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors utilized Perplexity to refine grammar points and language style in writing. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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