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Phytoestrogens and Sirtuin Activation for Renal Protection: A Review of Potential Therapeutic Strategies

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ABSTRACT

Significant health and socio-economic challenges are posed by renal diseases, leading to millions of deaths annually. The costs associated with treating and caring for patients with renal diseases are considerable. Current therapies rely on synthetic drugs that often come with side effects. However, phytoestrogens, natural compounds, are emerging as promising renal protective agents. They offer a relatively safe, effective, and cost-efficient alternative to existing therapies. Phytoestrogens, being structurally similar to 17-β-estradiol, bind to estrogen receptors and produce both beneficial and, in some cases, harmful health effects. The activation of sirtuins has shown promise in mitigating fibrosis and inflammation in renal tissues. Specifically, SIRT1, which is a crucial regulator of metabolic activities, plays a role in protecting against nephrotoxicity, reducing albuminuria, safeguarding podocytes, and lowering reactive oxygen species in diabetic glomerular injury. Numerous studies have highlighted the ability of phytoestrogens to activate sirtuins, strengthen antioxidant defense, and promote mitochondrial biogenesis, playing a vital role in renal protection during kidney injury. These findings support further investigation into the potential role of phytoestrogens in renal protection. This manuscript reviews the potential of phytoestrogens such as resveratrol, genistein, coumestrol, daidzein, and formononetin in regulating sirtuin activity, particularly SIRT1, and thereby providing renal protection. Understanding these mechanisms is crucial for designing effective treatment strategies using naturally occurring phytochemicals against renal diseases.

Introduction

Renal diseases are responsible for harmful health conditions and poor quality of life, and their care is also costly, making them a severe public health issue with an extreme incidence of mortality [1, 2]. In a multinational survey conducted in 2016, 42 out of 116 countries responding regarded chronic kidney disease (CKD) as a health care priority [1]. Lack of funding, services, and necessary infrastructures related to the care of patients with renal disease further exacerbate the condition [3]. Renal dysfunction also increases the risk of other metabolic diseases such as diabetes, cardiovascular complications, and hypertension [4]. Globally, every year, 5–10 million individuals succumb to kidney diseases, and it kills as many people as cancer, respiratory diseases, or diabetes kill annually [4]. Hypertension, malnutrition, obesity, diabetes, infectious diseases like malaria, tuberculosis, HIV infection, urinary tract infection, and leishmaniasis are responsible for causing kidney diseases [4, 5]. Currently, the different medications available for the treatment of kidney diseases, including renin-angiotensin-aldosterone system inhibitors, can cause serious health effects, such as hyperkalemia, by impeding the excretion of potassium [6].

The side effects of existing drugs, high cost of medicine as well as services for kidney diseases have opened avenues for exploring new, safe, effective, and cheap alternative drugs. In this regard, naturally occurring phytochemicals can be a promising alternative. Phytoestrogens are one such group of molecules that have proven beneficial health effects on patients with renal diseases.

Phytoestrogens are a diverse group of plant molecules found in different foods and are enriched in soy. They derive their name from their structural similarity with the primary female sex hormone 17-β-estradiol (E2). This structural similarity imparts on them the ability to bind estrogen receptors, causing antiestrogenic effects. Plants are known to use phytoestrogens for their natural defense against the overgrazing of animals. They control the female fertility of herbivore animals and thus prevent their overpopulation [7]. The sheep grazing on red clover fields that are rich in isoflavone and zoo animals feeding on an isoflavone-rich diet were known to face fertility issues because of the presence of phytoestrogens in their diet [8–11].

However, besides these harmful effects, phytoestrogens are also known to possess many health beneficial effects. They are the natural alternative to estrogen, known to reduce menopausal risks like osteoporosis in females, and are marketed for hormone replacement therapy and as dietary supplements. They were also found to be protective for various metabolic syndromes like obesity, type 2 diabetes, cardiovascular diseases, neurodisorders, and various forms of cancers such as breast, bowel, and prostate [7, 12–17]. Japanese people possess a lower incidence of chronic diseases compared to the Western population because of their diet rich in soy isoflavones, which had increased the world's attention towards soy isoflavones. However, phytoestrogens are also known as endocrine disruptors and have deleterious health effects, making their health benefits controversial [18–20]. More studies are required to resolve the beneficial or harmful effects of phytoestrogens.

Various phytoestrogens known to promote beneficial health effects, like resveratrol, genistein, and prunetin, are known to regulate gene expression by changing the expression/activity of longevity proteins called sirtuins. Sirtuins are nicotinamide adenine dinucleotide-dependent deacetylases with variable cellular targets (both histones and non-histone proteins) and have been observed to be beneficial in curing different diseases such as cancer, cardiovascular diseases, and diabetes [21–23]. A sirtuin isoform, SIRT1, plays a crucial role in regulating the metabolism of glucose and lipids. It was found to be renoprotective in various *in vitro* and *in vivo* models of renal impairment, mainly because of its antioxidant and anti-fibrotic effects, mitochondrial function regulation, and energy metabolism. Sirtuins mediate epigenetic regulation of gene expression by deacetylating histone proteins, thus affecting gene expression and renal functions. In a diabetic nephropathy mice model, decreased expression of SIRT1 was observed and overexpression of the *SIRT1* gene in proximal tubules suppressed albuminuria [24]. The abnormality in nicotine metabolism with decreased SIRT1 expression was suggested as a cause for increasing albuminuria and progressive kidney disease [24].

Sirtuin activating compounds are, therefore, in prime focus and emerging as critical targets for developing new therapeutic strategies against renal metabolic complications. Many sirtuin-activating phytoestrogens like resveratrol and genistein possess the full possibility for treating kidney diseases and thus can be potentially explored. Therefore, the present review aims to highlight the sirtuin-activating potential of phytoestrogens and their role in preventing/curing kidney diseases.

We conducted a systematic search in January 2024 across three databases, Google Scholar, Web of Science, and PubMed, to find potentially relevant studies. The search utilized key words related to SIRT and phytoestrogens, including phrases like "SIRT and phytoestrogen", "SIRT and renal health", "natural compounds", "phytoestrogens and health benefits", "kidney disease and Genistein", "Formononetin", "resveratrol", "phytochemicals", "renal protective effects of phytoestrogens", and "phytoestrogens as novel sirtuin modulators with renal protective activity". The studies included had to meet the following criteria: (1) published in English, (2) original research or review articles (excluding conference proceedings), and (3) no duplicates. Any ambiguous findings were discussed among the authors to reach an agreement. The search yielded 723 potentially relevant papers, of which 179 met the selection criteria and are presented in this review.

Sirtuins: In Brief

The enzyme family known as sirtuins (▶ **Tables 1** and **2**) is dependent on the cofactor NAD+ and is involved in a wide variety of key biological processes. These functions include metabolism, aging, and the response to stress. In accordance with the amino acids in their composition as well as enzymatic activity, the seven members of the sirtuin family found in humans can be divided into four distinct classes [25, 26]. SIRT1, SIRT2, SIRT3, SIRT4, SIRT5, SIRT6, and SIRT7 are the seven members of the sirtuin family in humans. SIRT1, SIRT2, SIRT3, and SIRT7 belong to class I and IV, respectively, while SIRT4 and SIRT5 belong to class II and III, respectively [27]. The structure and function details of these sirtuins are as follows:

SIRT1: SIRT1 (UniProt ID: Q96EB6) is a protein composed of 747 amino acids. Its structure includes a catalytic domain spanning from residues 234 to 510 and a C-terminal regulatory region from residues 641 to 665, forming a heterodimeric complex [28]. This complex features a Rossmann fold that facilitates NAD^+ binding. SIRT1 exhibits significant deacetylase activity and plays a multifaceted role in cellular processes, including antiaging, cancer protection, neurodegeneration delay, DNA repair, and the oxidative stress response [29]. Additionally, it modulates various cellular pathways, enhancing its importance in maintaining cellular homeostasis and protecting against age-related diseases [30, 31].

SIRT2: SIRT2 (UniProt ID: Q8IXJ6) comprises 389 amino acids and features a larger Rossmann fold domain coupled with a smaller zinc-binding domain. This structure includes a large groove and distinct structural variations [32]. SIRT2 functions as both a mono-ADP-ribosyl transferase and deacetylase, regulating glycolysis, tubulin acetylation, and playing a role in cancer and neurodegeneration. Its activity impacts metabolic reprogramming and cellular stability, underscoring its significance in health and disease [33, 34].

SIRT3: Human SIRT3 (UniProt ID: Q9NTG7) consists of 399 amino acids and exhibits a two-domain structure with a Rossmann fold, essential for NAD^+ binding. Activation of SIRT3 requires mitochondrial targeting and cleavage of its 101 N-terminal residues [35]. It possesses both deacetylase and mono-ADP-ribosyl transferase activities, which are crucial for mitochondrial func-

▶ **Table 1** Sirtuin family in brief [24–49].

Sirtuin	Classification	Enzyme activity	Location	Key functions	Main substrates	Rossmann fold	Bond interactions
SIRT1	Class I	Deacetylase	Nucleus and cytoplasm	Stress response, metabolism, aging	p53, FOXO, PGC-1α, NF-κB	Contains a classic Rossmann fold with alternating β-strands and α-helices that form a NAD+ binding pocket.	Key hydrogen bonds with NAD+ stabilize binding and allow deacetylation.
SIRT2	Class I	Deacetylase,demyristoylase	Cytoplasm and nucleus	Cell cycle regulation, cytoskeleton	α-Tubulin, FOXO1	Features a similar Rossmann fold crucial for NAD+ interaction.	Hydrogen bonds and hydrophobic interactions maintain structure, enabling regulation of acetylation states.
SIRT3	Class I	Deacetylase	Mitochondria and cytoplasm	Mitochondrial metabolism, ROS defense	IDH2, SOD2, LCAD	Employs a Rossmann fold for effective NAD+ binding.	Interactions include hydrogen bonds between NAD+ and active site residues, vital for mitochondrial functions.
SIRT4	Class II	ADP-ribosyltransferase, deacetylase, lipoamidase	Mitochondria	Insulin secretion, lipid metabolism	GDH	Has a Rossmann-like domain, functioning primarily as an ADP-ribosyltransferase.	NAD+ binding facilitates ADP-ribosylation, showcasing versatility of the Rossmann fold.
SIRT5	Class III	Deacetylase, desuccinylase, demalonylase	Mitochondria	Urea cycle, fatty acid oxidation	CPS1	Displays a Rossmann fold critical for binding NAD+, with a unique arrangement that supports its enzymatic role.	Stabilized by hydrogen bonds and hydrophobic interactions, essential for demalonylation and desuccinylation.
SIRT6	Class IV	Deacetylase, ADP-ribosyltransferase	Nucleus and endoplasmic reticulum	Genomic stability, glycolysis, inflammation	Histones H3K9, H3K56	Contains a Rossmann fold with structural features that support both NAD+ binding and interaction with other substrates.	Intricate hydrogen bonding networks with NAD+ support DNA repair and glucose metabolism.
SIRT7	Class IV	Deacetylase	Nucleus and cytoplasm	Ribosomal biogenesis, protein synthesis	Histone H3K18	Features a Rossmann fold tailored for NAD + interaction, primarily localized in the nucleolus.	Hydrogen bonds and van der Waals forces stabilized NAD+ binding, crucial for rRNA processing.

tion, cancer suppression, and metabolic regulation [36]. The roles SIRT3 in maintaining cellular energy balance and mitigating oxidative stress are central to its function [37].

SIRT4: SIRT4 (UniProt ID: Q9Y6E7) comprises 314 amino acids, but its crystal structure remains unreported in structural databases. This sirtuin acts primarily as a mono-ADP-ribosyl transferase, with a role in regulating glutamate metabolism and mitotic cell division [38]. SIRT4 is involved in various cancers, inflammation, and cellular stress responses, highlighting its potential as a therapeutic target [39].

SIRT5: SIRT5 (UniProt ID: Q9NXA8) has 310 amino acids and features a structure similar to other sirtuins, including a Rossmann fold and a zinc-binding domain, but with unique structural variations [40]. It shows weak deacetylase activity and is implicated in cancer growth, reactive oxygen species (ROS) elimination, and energy metabolism. Its unique structural features and functional roles contribute to its involvement in cancer and metabolic processes [41–43].

SIRT6: SIRT6 (UniProt ID: Q8N6T7) consists of 355 amino acids and includes two globular domains with a large Rossmann fold for NAD+ binding and a zinc-binding motif with some variations from other sirtuins [44]. SIRT6 functions as a mono-ADP-ribosyl transferase, playing critical roles in telomere maintenance, DNA repair, aging, and inflammation [45]. Its activity is essential for maintaining genomic stability and regulating cellular responses to stress [46].

SIRT7: SIRT7 (UniProt ID: Q9NRC8) contains 400 amino acids and features an N-terminal domain with three helices, which is in-

▶ **Table 2** Experimental works on the sirtuin family, at a glance.

	Target	Experiment/mechanism	Outcome	Ref.
SIRT 1	Vascular calcification	Spermidine increased SIRT1 expression.	Revealed that spermidine lowers vascular calcification in chronic kidney disease by raising SIRT1 expression and decreasing stress, which may lead to a therapeutic treatment.	[156]
	Renal injury and fibrosis	SSR's potential to reduce kidney damage and fibrosis through modulating the NLRP3 inflammasome and SIRT1/Smad3 deacetylation.	Renal damage and fibrosis in the kidneys that were left behind were greatly reduced by Shen Shui IIRecipe (SSR). Furthermore, SSR efficiently suppressed inflammatory infiltration, upregulated the Sirt1/Smad3 deacetylation pathway, and prevented activation of the NLRP3/ASC/caspase-1/IL-1 cascade.	[157]
	Chronic kidney disease (CKD)	Resveratrol enhanced SIRT1-FoxO1 engagement and decreased FoxO1 acetylation.	FoxO1 is likely targeted by SIRT1, which plays a crucial role in mediating the protective effects of resveratrol on the kidneys of rodents with chronic kidney disease.	[158]
	Muscle atrophy	Resveratrol decreased proteinuria and cystatin C in 5/6-nephrectomized (5/6Nx) rats.	FoxO1 may be an intermediate of SIRT1 and play an essential part in muscle degeneration in chronic renal disease. Resveratrol improves renal fibrosis by inhibiting the production of TGF-β and connective tissue growth factor (CTGF).	[159]
	Diabetic kidney disease (DKD)	This work used high-glucose cultured diabetic rat mesangial cells (RMCs) pretreated with metformin or transfected with AMPK, SIRT1, and FoxO1.	Metformin reduced oxidative stress, enhanced autophagy, and slowed cell growth in high-glucose cultured RMCs via the AMPK/SIRT1-FoxO1 pathway in diabetic rats and high-glucose cultured RMCs.	[160]
	Renal ischemia (RI)	Genistein's preventive action on renal RI injury.	Genistein administration led to a rise in renal SIRT1 expression. The protective impact of genistein against kidney failure, cell death, and proliferation after RI injury was dramatically abolished by the pharmacological suppression or shRNA-mediated reduction of SIRT1.	[161]
	Neuroprotection	Quercetin may also strengthen the body's natural defenses against oxidative stress.	Inducing autophagy and activating sirtuins (SIRT1) may be how quercetin exerts its neuroprotective effects.	[162]
SIRT2	Renal fibrosis	UUO mice and tubulointerstitial fibrosis patients upregulated SIRT2 in the tubulointerstitium. SIRT2 suppression enhanced tubulointerstitial fibrosis.	Involvement of SIRT2 in fibroblast activation and tubulointerstitial fibrosis, mediated by control of the MDM2 pathway, suggests that targeting SIRT2 as a treatment strategy for renal fibrosis is justified.	[163]
	Renal inflammatory injury	Important function in renal inflammatory damage. Both mRNA and protein levels of CXCL2 and CCL2 were dramatically downregulated in the kidneys of LPS-treated SIRT2-/- animals.	Regulation of SIRT2 may be a significant treatment option against kidney inflammation injury due to its correlation with the expression of CXCL2 and CCL2 in the kidney.	[164]
	Autologous kidney stem cell-based organoid formation	The formation of kidney organoids relies on SIRT2-mediated canonical Wnt/-catenin signaling.	Stem cells of kidneys have the ability to generate kidney organoids by a *de novo* process.	[165]

continued next page

▶ **Table 2** *Continued*

	Target	Experiment/mechanism	Outcome	Ref.
SIRT3	Tubulointerstitial lesions in proteinuric kidney disease	SIRT3 reduced renal lipotoxicity-induced ROS and inflammation. SIRT3 improved mitochondrial oxidative capacity and antioxidant gene expression.	Tubulointerstitial abscesses in proteinuric kidney conditions benefit from SIRT3′s role in reducing inflammation caused by lipotoxicity and reactive oxygen species.	[166]
	Chronic kidney disease (CKD)	Rhein's antioxidant and antifibrotic properties led to enhanced renal function.	By stimulating the SIRT3/FOXO3 signaling pathway, rhein treatment enhanced kidney function.	[167]
	Chronic kidney disease (CKD)	JPYSF reduces renal fibrosis and improves renal function in rats with CKD.	The Jian-Pi-Yi-Shen formula (JPYSF) increased SIRT3 expression, inhibited mitochondrial fission, promoted mitochondrial fusion, and reduced oxidative damage in the kidneys of CKD rats.	[168]
	Diabetic nephropathy	Kaempferol was used to treat the HK 2 cells.	Kaempferol significantly raised transcription levels of SIRT3, pAkt/Akt ratio, and p-FoxO3a/FoxO3a ratio. Kaempferol increases SIRT3 and the ROS-sensitive Akt/FoxO3a signaling pathway to reduce HG-induced apoptosis and oxidative stress.	[169]
SIRT4	Acute kidney injury	FOXM1 suppressed NF-κB phosphorylation in HG-treated cells, while SIRT4 restored it.	Reducing kidney damage and podocyte pyroptosis in diabetic neuropathy is achieved by the transcriptional activation of SIRT4 and the inhibition of NF-κB signaling and the NLRP3 inflammasome.	[170]
	Diabetic nephropathy	SIRT4 overexpression.	Podocyte apoptosis is an early pathogenic process leading to diabetic nephropathy, and overexpression of SIRT4 inhibits both glucose-induced apoptosis and ROS generation.	[171]
SIRT5	Acute kidney injury	SIRT5 regulation on apoptosis caused by cisplatin in the human kidney.	SIRT5 protected human kidney HK-2 cells against apoptosis caused by cisplatin as well as mitochondrial dysfunction by means of controlling Nrf2/HO-1 and Bcl-2.	[172]
SIRT6	Diabetic kidney disease	The Yishen Tongluo formula's (YSTLF) effect on boosting TGF-1 breakdown and regulating the SIRT6/TGF-1/Smad2/3 pathway.	By modulating the SIRT6/TGF-1/Smad2/3 signaling pathway and encouraging the breakdown of TGF-1, YSTLF may drastically reduce kidney damage and fibrosis.	[173]
	Vascular calcification (vc)	Individuals having CKD with VC had significantly reduced levels of SIRT6 in both their PBMCs and radial artery tissue.	SIRT6 inhibited osteogenic transdifferentiation, which blocked vascular calcification.	[174]
	Chronic kidney disease	Boost SIRT6 gene expression.	Exosomes may have a protective impact against renal fibrosis if SIRT6 expression is boosted while β-catenin and its corresponding downstream substances are suppressed.	[175]
	DNA damage and podocyte injury of chronic kidney disease	Nrf2 knockdown could partially counteract SIRT6 activation's cytoprotective effects.	The SIRT6-Nrf2-HO-1 pathway was critical in protecting podocytes from further damage caused by Ang II-induced oxidative damage to DNA.	[176]
SIRT7	Hypertensive renal injury	Hypertension and hypertensive kidney damage may benefit from SIRT7 signaling.	SIRT7 helps prevent renal fibrosis, damage, and inefficiency caused by hypertension by promoting the KLF15/Nrf2 signaling pathway. This has the effect of lowering ferroptosis, which is the peroxidation of lipids.	[177]
	Acute kidney injury	Inhibition of SIRT7 protected HK-2 cells against apoptosis induced by cisplatin and reduced NF-κB (NF-κB) expression.	By increasing miR-142–5 p, which inhibits SIRT7/NF-B, p53 inhibition may reduce cisplatin-induced acute kidney injury.	[178]

volved in DNA binding [47]. This sirtuin has deacetylase activity and is crucial for the aging of hematopoietic cells, energy balance, ribosomal DNA transcription, and cancer regulation [48]. SIRT7′s involvement in these processes underscores its significance in cellular aging and cancer biology [49].

The sirtuin family of proteins is thus crucial for various cellular processes, and their dysregulation is linked to diseases like cancer, neurodegenerative disorders, and metabolic issues [50, 51]. The first identified sirtuin, Sir2 from yeast, affects lifespan; its deletion reduces longevity, while overexpression increases it. Sir2, a NAD+-dependent histone deacetylase, catalyzes deacetylation, producing nicotinamide and O-acetyl-ADP-ribose as by-products, with mammalian homologs known as sirtuins [52–54]. Initially thought to only deacetylate histones, sirtuins also modify non-histone proteins in mammals [23, 55–60].

SIRT1, a mammalian equivalent of Sir2, regulates lifespan and is upregulated by calorie restriction. SIRT1′s activation relies on NAD+, synthesized via *de novo* pathways from tryptophan and through a salvage pathway involving nicotinamide, where NAMPT is crucial [61]. Two forms of NAMPT exist: intracellular (iNAMPT) and extracellular (eNAMPT), with iNAMPT boosting SIRT1 activity by enhancing the NAD+ supply [62]. SIRT1, in turn, promotes NAD+ production through a feedback loop that modulates iNAMPT levels [63, 64]. Overexpressing iNAMPT in the liver reduces hepatic steatosis and improves glucose tolerance [65, 66] while calorie restriction elevates iNAMPT in muscle mitochondria [67].

Recent studies emphasize the role of SIRT1 in health, longevity, and disease prevention, marking it as a promising drug target [23, 60]. It regulates metabolic processes related to glucose, lipid, and energy metabolism via gene transcription [23]. While sirtuins have well-established antioxidant functions, some, like SIRT4, may induce oxidative stress [63]. SIRT1 dysregulation is implicated in metabolic and age-related diseases, including cardiovascular disorders, neurodegenerative diseases, and diabetes [22, 68–71].

The role of SIRT1 in insulin resistance is significant, as its targets include peroxisome proliferator-activated receptor (PPAR)-α, PPAR-γ, and uncoupling protein-1. Reduced SIRT1 activity impairs glucose and lipid metabolism [72]. Additionally, miR-155 can downregulate SIRT1 expression under high glucose conditions [73]. SIRT1 knockdown in adipose tissue increases, while overexpression decreases obesity in high-fat diet rats [74]. Liver-specific SIRT1 knockdown worsens insulin resistance, while systemic overexpression improves it [75–77], highlighting SIRT1′s critical metabolic regulatory role and the potential of sirtuin-activating compounds for addressing metabolic disorders.

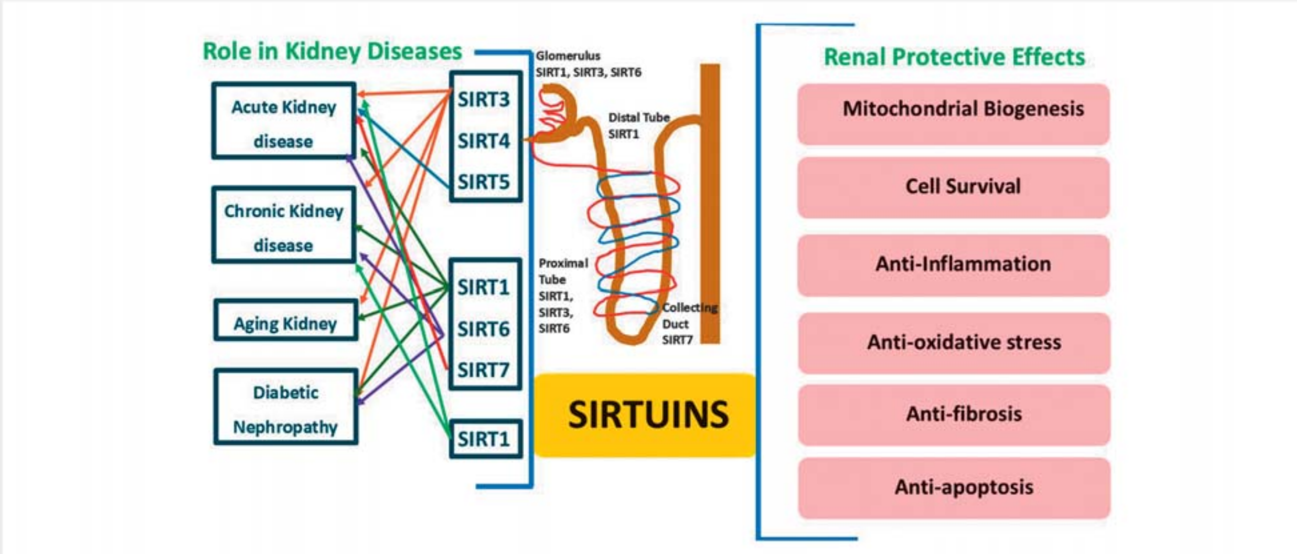
Renal protective activity of sirtuins

Recent studies have amassed a plethora of evidence to corroborate the important role of sirtuin in preventing the onset/progression of different life-threatening renal diseases (summarized in ▶ **Figs. 1** and **2**). The activation of sirtuins in the kidney prevents apoptosis and inhibits the fibrosis and inflammation of renal cells [73, 74]. Abnormal metabolism of lipids is associated with the onset and development of kidney diseases. SIRT1 positively regulates sterol-activated receptors like liver X receptors (LRXs) and farnesoid X receptors (FXRs), which are essential for the balanced metabolism of cholesterol and bile acid [74, 75]. Sirtuins also provide renal protection by assisting in the activation of autophagy, increasing the resistance to hypoxia, controlling sodium balance, and blood pressure [74, 76]. Studies have shown that the overexpression of SIRT3 decreases the inflammation and accumulation of ROS in a mouse model of tubulointerstitial inflammation [77].

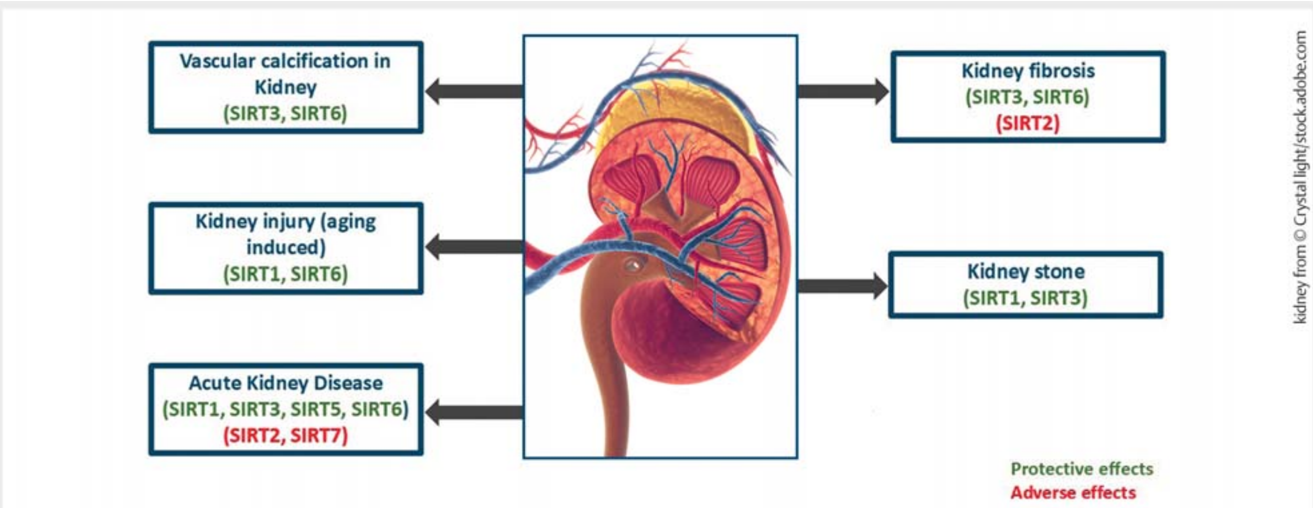
Sirtuins have shown the potential to ameliorate acute nephrotoxicity, one of the harmful side effects of the anticancer compound cisplatin. Sears et al. have shown that transgenic mice overexpressing SIRT1 in the proximal tubules were able to attenuate cisplatin-induced damages during acute kidney injury (cis-AKI) [75]. Cisplatin compromises both the function and number of peroxisomes and also increases the level of renal ROS, which eventually damages the kidney [75, 78]. The overexpression of SIRT1 in transgenic mice mitigated cis-AKI by rescuing the functions of peroxisomes, localizing catalase enzymes and inducing their activity, which is vital for the elimination of ROS and anti-apoptotic effects [75]. At the molecular level, SIRT1 overcomes acute kidney injury by deacetylating p53, PPAR-γ coactivator 1-alpha (PGC-1α), nuclear factor-κB (NF-κB) p65 subunit, and MAPK phosphatase-1, which increases mitochondrial biogenesis and mitochondrial respiration, which increases the expression of chemokines (CCL2 and CXCL2) through p65 promoter binding, thereby inducing an anti-inflammatory response [79, 80]. The activation of SIRT3 and AMP kinase by the glycoprotein stanniocalcin-2 (regulator of serum phosphate and calcium homeostasis) is involved in protecting from ischemia/reperfusion (I/R) injury. Sirtuins, therefore, protect from acute kidney injury by mediating the effective utilization of energy and activating anti-inflammatory and antioxidative responses.

Sirtuins SIRT1 and SIRT2 inhibit renal fibrosis by inhibiting phosphorylation of the signal transducer, activation of transcription 3 (STAT3), suppression of cyclooxygenase 2 expression, phosphorylation of epidermal growth factor receptor and platelet-derived growth factor receptor, and deacetylation of Smad4 [73, 81]. The suppression of inflammation and oxidative stress via decreased expression of cyclooxygenase-2 had been reported for the anti-fibrotic effect of SIRT1 [82]. Endothelial-specific knockdown of SIRT1 in mice impairs angiogenesis and decreases matrix metalloproteinase-14 expression in kidneys while SIRT1 overexpression restores the expression of matrix metalloproteinase-14 in mice, which improved the endothelium's matrilytic functions and angiogenesis, preventing renal fibrosis [83]. The deacetylation of Smad4 by SIRT1 led to decreased signaling through TGF-β, resulting in decreased cleavage of E-cadherin from the cell surface, thus reducing renal tissue fibrosis [84].

Sirtuins have also shown the ability to mitigate aging-associated problems in the kidneys. The increased expression of sirtuins due to calorific restriction had shown antiaging activity in aged kidneys by helping cells adapt to hypoxia via autophagy [85]. Chronic hypoxia is associated with aging-related mitochondrial dysfunction, which can eventually cause failure of the kidney [85, 86]. The SIRT1/forkhead box O3a (FOXO3) axis plays a significant role in extending lifespan through calorie restriction. The deacetylation of FOXO3 by SIRT1 increases the expression of a critical molecule, Bnip3 (BCL2/adenovirus E1B 19-kDa interacting protein 3), which promotes longevity and regulates mitophagy (removal of



▶ **Fig. 1** Sirtuins are essential for regulating a wide range of cellular activities in the kidney. In addition to promoting mitochondrial biogenesis, they help prevent apoptosis, fibrosis, inflammation, and oxidative stress. Different forms of sirtuins have different roles, and studies have shown that they can help with various kidney problems.



▶ **Fig. 2** Different members of the sirtuin family have different effects, but all of them are essential for renal functioning. The kidneys are protected from vascular calcification by SIRT3 and SIRT6. Furthermore, SIRT1 and SIRT6 have shown promise in preventing age-related kidney damage. Acute renal disease is an illness that can be prevented by SIRT1, SIRT3, SIRT5, and SIRT6, although SIRT2 and SIRT7 have been found to cause harm. SIRT1 and SIRT3 prevent kidney stones. SIRT1, SIRT3, and SIRT6 protect against kidney fibrosis, while SIRT2 is harmful.

defective mitochondria) [85]. SIRT1 activator also reduces the aged kidney's vulnerability to acute stress by suppressing cell apoptosis [87]. The inactivation of NF-κB by SIRT1-mediated deacetylation has been implicated in suppressing the expansion of mesangial cells and podocyte dysfunction, which is vital for the excretion of proteins during urination [88–90]. In the kidneys of diabetic kidney disease (DKD) patients, low expression of SIRT1 has been found. The overexpression of SIRT1 in a mice model of type 1 diabetes mitigated injury to podocytes and inhibited the progression of DKD with concomitant deacetylation of different transcription factors like FOXO, STAT3, p53, and PGC-1α [91, 92].

Natural sirtuin agonists have emerged as promising therapeutic agents for kidney disorders due to their ability to regulate sirtuin activity. Most sirtuin activators are polyphenolic compounds, with resveratrol being the first identified natural SIRT1 activator [93]. Resveratrol has been shown to attenuate proteinuria, reduce malondialdehyde levels, and enhance renal function in diabetic mice by increasing renal cortical Mn-SOD activity and inhibiting apoptosis in glomerular podocytes and renal tubular epithelial cells (RTECs). It also mitigates excess ROS production and improves mitochondrial function by enhancing respiratory chain activity and preserving mitochondrial integrity [94]. Other natural compounds like curcumin, silybin, honokiol, and quercetin also regulate sirtuins, with curcumin activating the SIRT1/Nrf2/HO-1 pathway to combat oxidative stress and delay kidney damage [95]. Silymarin protects against cisplatin-induced RTEC apoptosis through SIRT3 activation [96], while honokiol restores SIRT3 expression and mitochondrial function in RTECs [97]. Quercetin reduces RTEC senescence and alleviates renal fibrosis via SIRT1-mediated mitochondrial phagocytosis. Additionally, isoliquiritigenin, a natural flavonoid, protects against DKD by regulating the MAPK and Nrf-2 pathways, thereby mitigating inflammation and oxidative stress [98, 99].

On the synthetic side, compounds like SRT1720, SRT3025, and MDL-800 have been developed to activate sirtuins, particularly SIRT1 and SIRT6. SRT1720 has shown potential in reducing p65 acetylation and improving renal function in high glucose-induced podocyte epithelial-mesenchymal transition (EMT). SRT3025 reverses TGF-β1-induced collagen production and renal fibrosis [100]. MDL-800, a SIRT6 activator, has demonstrated efficacy in reducing tubulointerstitial inflammation and fibrosis in obstructive nephropathy models [101].

Moreover, strategies to enhance NAD+ levels, crucial for sirtuin activation, include supplementation with NAD+ precursors like nicotinamide mononucleotide (NMN) and nicotinamide riboside (NR). NMN has been shown to improve SIRT1 function and mitigate the progression of DKD by epigenetically regulating claudin-1 expression [102, 103]. Overall, the interplay between natural and synthetic sirtuin activators highlights their potential in developing innovative therapies for kidney disorders, underscoring the importance of sirtuins in renal health. Hydrogen sulfide was also found to protect renal tissue from diabetes-associated damage by increasing SIRT1 activity [104].

However, sirtuins have also been found to promote kidney cyst formation. The deacetylation of p53 and Rb by SIRT1 induces the proliferation of renal epithelial cells. The continuous growth of epithelial cells promotes cyst formation, resulting in polycystic kidney disease. The lack of SIRT1 in mice or SIRT1 inhibitor administration decreased the rate of cyst formation [105]. SIRT2 overexpression is also linked with the progression of polycystic kidney disease [105]. In a Pdk1 knockout model of mice, SIRT2 overexpression causes polyploidy, amplification of aberrant centrosome, and disrupts cilia formation, promoting kidney disease [106]. Whereas, in situations like (I/R) injury, where the apoptotic loss of epithelial cells results in damaging the kidney, the recovery can be achieved by the administration of SIRT1 activators. Therefore, the individual's diseased background governs the favorable or unfavorable effects of sirtuins on different kidney diseases.

Health Beneficial Effects of Phytoestrogens

Phytoestrogens are plant-based dietary molecules that are structurally similar to the primary female sex hormone estradiol and can act either as agonists or antagonists to the estrogen receptor [20, 107]. Phytoestrogens include various structurally different natural compounds such as flavonoids, lignans, prenylflavonoids, coumestans, isoflavonoids, erythroidine alkaloids, and stilbenes [20, 107]. Genistein and daidzein found in *Glycine max*, coumestrol found in alfalfa, pinto beans, split peas, and clover sprouts, as well as 8-prenylnarigenin found in *Humulus lupulus* are some of the widely studied phytoestrogens. Arctigenin from *Arcticum lappa*, triginelline from coffee, tanshinone II A from *Salvia miltiorhizza*, diarylheptanoid from *Curcuma comosa*, and an erythroidine alkaloid found in *Erythrina poeppigiana* have also shown estrogenic activity [107].

Studies have shown that phytoestrogens possess both beneficial and harmful health effects. The intake of phytoestrogens had not convincingly shown beneficial effects in alleviating menopausal symptoms. Only in a few studies was it shown that phytoestrogen intake maintains bone mineral density and reduced hot flushes. The intake of genistein has shown to improve the metabolism of glucose and reduce insulin levels [20, 108]. Interaction with estrogen receptors affecting the epigenome, activation of AMP-activated protein kinase, activation of PPAR, and ARE/EpRE are some of the ways by which different phytoestrogens exert their health-promoting effects [20]. Generally, phytoestrogens have shown the ability to reduce the risk of lung cancer, prostate cancer, thyroid cancer, ovarian cancer, and breast cancer in postmenopausal women [20, 107]. Overall, the use of phytoestrogens has shown encouraging results, but there is a lack of convincing clinical evidence to strongly underpin the consumption of phytoestrogens as anticancer agents [107]. Phytoestrogens have also been shown to play an essential role in decreasing the risk of cardiovascular diseases and cerebral infraction, improving cognition, and protecting the cerebral cortex [20]. However, phytoestrogens may also act as endocrine disruptors and have harmful effects on health. Though phytoestrogens have shown various possible beneficial health effects, there are insufficient data to conclusively prove that the benefits outweigh the risks.

The beneficial role of dietary phytoestrogens is also suggested for metabolic syndrome like type 2 diabetes [13, 14, 109, 110]. Genistein and soy isoflavone supplementation had been reported to improve glucose metabolism and insulin resistance in women after menopause [111]. Nutritional intervention by increasing the intake of flaxseeds and soy isoflavones decreases insulin resistance and improved control of glucose levels in both animal models as well as humans [13, 14, 17]. However, it is not clear whether the observed beneficial effects are due to phytoestrogens or other dietary components. The activation of PPAR family proteins like PPARα and PPARγ by phytoestrogens like isoflavones and formononetin has been suggested to provide beneficial effects on metabolic syndromes, obesity, and diabetes [17]. Studies have also demonstrated that the modulation of immune responses by dietary phytoestrogens like daidzein is responsible for improving metabolic functions [112]. Genistein and resveratrol also proved promising to prevent postmenopausal obesity by attenuating hepatic lipogenesis and inflammation and improving the antioxidant capacity of plasma [113, 114]. However, the effective physiological concentrations and long-term effects of phytoestrogens on metabolic syndromes need to be established.

Renal protective effects of phytoestrogens

The consumption of dietary phytoestrogens is evidenced to retard the development of renal diseases (summarized in ▶ **Fig. 2**). The inclusion of dietary flaxseeds and soy reduces cyst development and damage to renal parenchyma in polycystic kidney disease (PKD) [115]. This effect was found to be more profound in female rats with PKD, which were fed with a low-protein diet [116]. Resveratrol, an activator of PPAR-γ coactivator-1 alpha (PGC-1α), was found to prevent acute renal injury by decreasing apoptosis and oxidative stress [117]. The protective effects of resveratrol to improve kidney function and structure are due to a reduction in renal fibrosis, oxidative stress, mesangial expansion, and cytokine levels [118]. It reduces the proliferation of fibroblasts to maintain the structure of the kidney [119]. It increases apoptosis in renal cancer cells and reduces cell growth and migration [120].

Genistein (20 mg/kg/day) treatment, either alone or in synergistic combination with metformin (50 mg/kg/day), decreases the serum level of inflammatory cytokines (TNF-α, interleukin-6, and C-reactive protein) and downregulates inflammatory responses in diabetic rats (alloxan induced). The genistein treatment resulted in achieving normoglycemia and significantly improved kidney function biomarkers compared to rats treated with metformin alone [121]. Formononetin treatment for 16 weeks (40 mg/kg) was also found to be renoprotective and significantly improved the creatinine clearance rate and plasma concentration of blood urea nitrogen and creatinine in type 2 diabetic rats [122]. It also alleviated the nephrotoxic effects of cisplatin by sequestering ROS and reducing chromatin condensation. Furthermore, it inhibited cisplatin-induced phosphorylation of JNK, caspase-3, and caspase-8 cleavage to prevent cell death [123].

The renoprotective effects of genistein in diabetic rats are due to activation of the Nrf2-HO-1/NQO1 pathway, which inhibits oxidative stress, and by overpowering the TGF-β1/Smad3 pathway, which decreases renal fibrosis [124]. It was also found to inactivate mTOR signaling to induce autophagy in renal podocytes stressed with high glucose conditions or chloroquine [125]. Daidzein treatment maintained homeostasis of Pi and $Ca2+$ in the kidneys of a andropause rat model, thus improving bone health and also increased the expression of the antiaging protein Klotho in these animals [126]. Biochanin A is also a potent nephroprotective agent that protects cisplatin-induced renal injuries by reversing inflammatory and apoptotic activities [127]. It was also found effective in reversing renal changes in postmenopausal women and thus can be used as a replacement for estrogen therapy. The deceased renal expression of TNF-α and iNOS by biochanin A was suggested for providing renal protection in postmenopausal women [128]. However, in-depth mechanistic studies and combination therapies for attenuating kidney diseases mainly targeting human subjects are limited.

Phytoestrogens as novel sirtuin modulators with renal protective activity

Much attention has been levied to the identification of SIRT 1 activators for their significant role in regulating metabolism and aging, as they have multiple protein targets to deacetylate in different tissues, including kidneys. Phytoestrogens have shown the property to stimulate the activity of sirtuins, and different studies (as stated above) have shown the significant role of sirtuins in preventing the onset and progression of different renal diseases. Thus, phytoestrogens can be potential agents to activate sirtuins and provide renal protective activity. Mitochondrial biogenesis improves the oxidation of fatty acids and strengthens the antioxidant defense. It helps to mitigate the fatty acid load, hypoxia, and aging-related injuries [129]. These factors are involved in the progression of acute and CKDs, and previous studies have shown the ability of sirtuins to control these factors and provide renal protection [129]. Thus, it suggests that the activation of SIRT1 by phytoestrogens can provide renal protection (▶ **Table 3** and **Fig. 3**). Phytoestrogens, found in plants, activate sirtuins while also balancing hormones and providing antioxidant benefits, making them safer and potentially more effective than synthetic SIRT agonists. Their natural origin lowers the risk of side effects, promoting overall health. SIRT1 activation and renal protective activities of some phytoestrogens are discussed below.

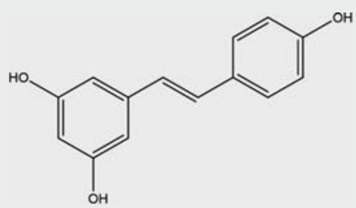
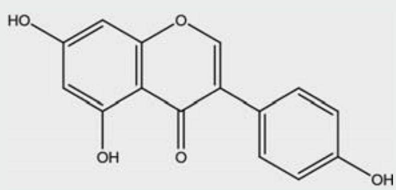
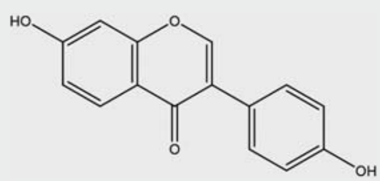
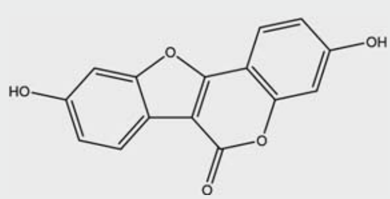
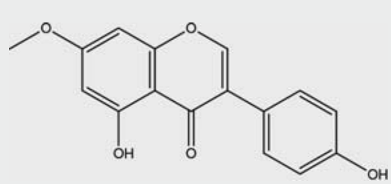
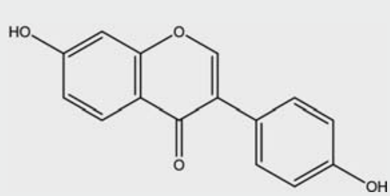
Resveratrol

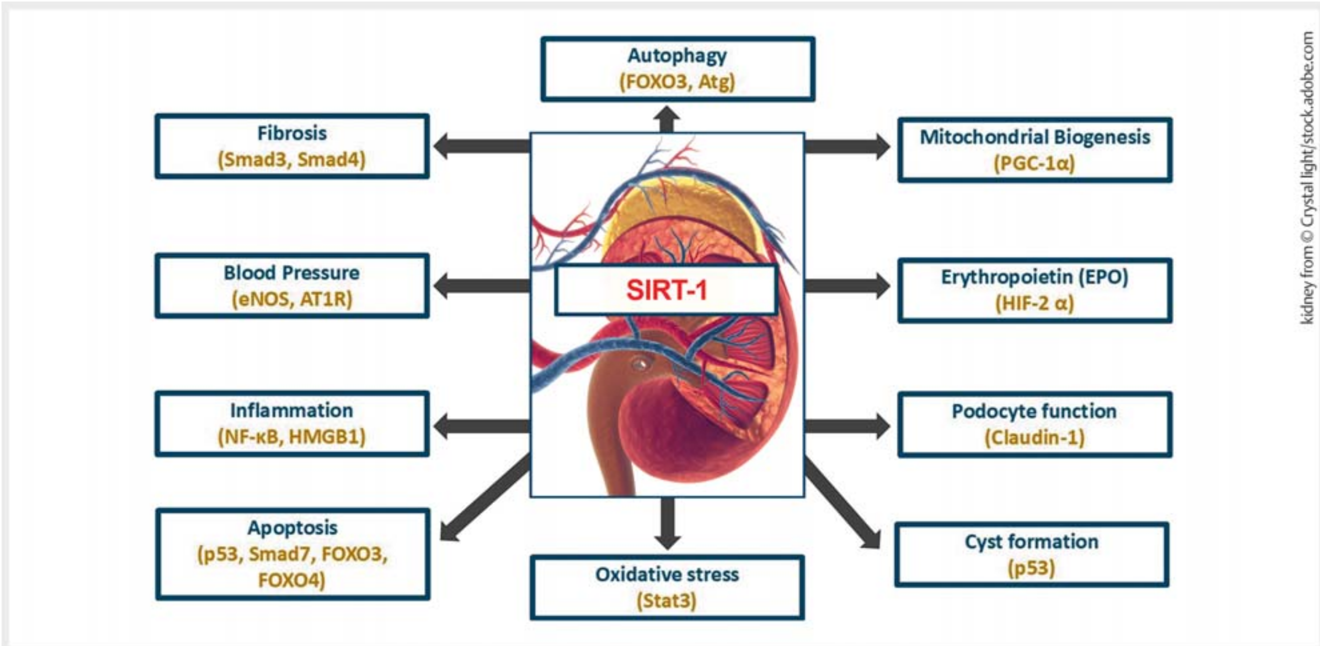
Resveratrol is the most studied phytoestrogen, which is known to activate SIRT1 and regulate glucose and lipid metabolism. It is also known to exert renoprotective effects and many other health beneficial effects, mainly by modulating inflammatory and oxidative stress responses. In an animal model of diabetic nephropathy, resveratrol treatment reduced proteinuria and depositions in the extracellular matrix with renoprotective effects [130]. The activation of SIRT1 and its downstream gene targets FOXO and PGC-1α were suggested to increase mitochondrial function in skeletal muscle and myocardium [131, 132]. Resveratrol treatment improves mitochondrial function in high glucose-challenged podocytes by activating the SIRT1/PGC-1α pathway [132]. However, the protective effects of resveratrol in reducing renal fibrosis are only observed at its lower doses while the higher doses were found to aggravate renal fibrosis. In one study, treatment of HK-2 cells (human tubular epithelial cells) with 5–20 µM of resveratrol led to SIRT1-mediated Smad3/Smad4 deacetylation, which decreased TGF-β-induced transition of epithelial to mesenchymal cells and thus decreased renal fibrosis. However, higher doses of resveratrol (≥ 40 µM) promoted mitochondrial oxidative stress, cytoskeleton distortion, and loss of anti-fibrotic activity [133]. Therefore, the careful examination of the resveratrol dose is required to observe its protective effects.

Genistein

Genistein (4,5,7-trihydroxyisoflavone) is another extensively studied nonsteroidal polyphenolic isoflavone found in soy. Studies have shown that genistein ameliorates conditions like inflammation, apoptosis, and cancer [134]. It was found to be nephroprotective and protects mice from radiation-induced nephrotoxicity [135]. Genistein also has implications for clinical treatment as it possesses many beneficial properties like low toxicity. The physiological effects of genistein are closely related to its SIRT1 activating properties. In the models of oxidized low-density lipoprotein-induced injury in human umbilical vein endothelial cells, genistein was able to reduce the production of superoxide anion synthesized due to endothelial nitric oxide synthase by enhancing the expression of SIRT1 [136]. Similarly, in another study by Zhang et al.

▶ **Table 3** SIRT1 targets and renoprotective effects of phytoestrogens.

S. No.	Phytoestrogen	SIRT1 downstream target	Cellular effect	Renal protection
1.	**Resveratrol** 	FOXO1 PGC-1*α* Smad3/Smad4 [131–132]	Improve mitochondrial function [132] Decrease TGF-*β* signaling [133]	Reduce renal fibrosis
2.	**Genistein** 	Inhibit TNF-*α* [138]	Anti-inflammatory [134] Increase the activity of antioxidant enzymes [137]	Protect nephrotoxicity
3.	**Daidzein** 	PGC-1*α* [140]	Mitochondrial biogenesis [140]	Prevent renal proximal tubular cell injury
4.	**Coumestrol** 	NAD^+/NADH ratio [142]	Mitochondrial biogenesis [142]	Prevent renal injury
5.	**Prunetin** 	NF-*κ*B [144]	Anti-inflammatory [143]	Prevent renal injury
6.	**Formononetin** 	HMGB1 [149]	▪ Antioxidative [146] ▪ Anti-inflammatory ▪ PPARγ agonist [148, 151]	Improves diabetic kidney disease



▶ **Fig. 3** Function of SIRT1 in renal protection. SIRT1 protects the kidneys through multiple methods. SIRT1 inhibits kidney fibrosis by interrupting the TGF-β/Smad pathway and inhibiting Smad3 and Smad4, reducing fibrosis. SIRT1, eNOS, and AT1R also control renal blood pressure subtly. SIRT1 and eNOS reduce blood pressure and vasodilation, although AT1R activation increases it. In balance, SIRT1 may regulate eNOS-mediated vasodilation and AT1R-mediated vasoconstriction. SIRT1's anti-inflammatory characteristics can reduce the inflammatory effects of HMGB1 and help manage renal inflammation by negatively regulating NF-κB, a critical component in inflammation. To prevent renal cell death, SIRT1 suppresses p53, FOXO3, and FOXO4, while Smad7 counteracts TGF-β-mediated apoptosis. SIRT1's antioxidant activities may reduce renal oxidative stress via STAT3-mediated mechanisms. SIRT1's protective action against oxidative stress may increase Rb/p53 activity to prevent abnormal cell proliferation in renal cysts. However, blocking this route may cause excessive cell proliferation and cyst formation. The context and cellular conditions determine the correlation. SIRT1's positive connection with claudin-1 implies it may increase renal podocyte function and maintain the glomerular filtration barrier. SIRT1 and erythropoietin (HF2α) may improve kidney cellular resilience, lowering inflammation, oxidative stress, and cell death. The positive connection between SIRT1 and PGC-1α in the renal region suggests their collaboration in promoting mitochondrial biogenesis, leading to improved kidney function and energy metabolism. SIRT1's positive connection with FOXO2 and ATG shows its coordinated autophagy control, which is essential for cell homeostasis and damage removal.

[137], genistein increased the activity of different antioxidant enzymes such as superoxide dismutase, glutathione, catalase, and glutathione peroxidase and reduced the levels of malondialdehyde and ROS by increasing the expression of SIRT1 [137]. The coadministration of genistein and daidzein was able to inhibit TNF-α-mediated muscular atrophy in the C2C12 muscle cell line by boosting the expression of SIRT1 [138]. Genistein protects from I/R-induced renal injury by activating SIRT1. A significant reduction in cell death (I/R induced) and stimulation of cell proliferation with upregulated renal SIRT1 expression was observed after genistein administration in mice. However, these protective effects of genistein were reversed after depletion of SIRT1 (either shRNA mediated or pharmacological inhibition), highlighting the indispensable role of SIRT1 in mediating renoprotective effects of genistein [139].

Daidzein

Daidzein, another phytoestrogen found in soybeans, has shown the ability to activate SIRT 1 and increase mitochondrial biogenesis. Toxins, hypoxia, and trauma are known to cause mitochondrial damage [140]. Phytoestrogens like daidzein and formononetin were shown to increase mitochondrial biogenesis by activating SIRT1 and increasing the expression of PGC-1α after renal proximal tubular cell injury [140]. Daidzein treatment also improved the mitochondrial biogenesis necessary for energy metabolism in muscles by increasing the expression of mitochondrial transcription factor A and Cox1 and Cytb mitochondrial genes. In improving the mitochondrial biogenesis by daidzein, SIRT1 was shown to play an important role [141].

Coumestrol

Another phytoestrogen, coumestrol, an isoflavone, has also been able to activate the biogenesis of mitochondria by SIRT1 activation. It was found to elevate the intracellular ratio of NAD (+)/NADH, which is responsible for activating SIRT1 in myocytes. Coumestrol treatment induces the expression of the electron transfer chain proteins in mitochondria and increases total mitochondrial contents in myocytes. It also increases ATP concentration and improves the function of myocytes. These beneficial effects of coumestrol were abolished by diminishing SIRT1 by either incubating cells with siRNAs or a SIRT1 inhibitor, suggesting the critical role of SIRT1 in coumestrol-induced mitochondrial biogenesis [142].

Prunetin

Prunetin, another phytoestrogen found in soy, has many beneficial health effects. It possesses anti-inflammatory properties and inhibites LPS-induced production of inflammatory cytokines in nasal epithelial cells of humans [143]. It also inhibits LPS-induced production of nitric oxide by suppressing iNOS and prostaglandin E2 by suppressing COX-2 expression. It also modulates NF-κB signaling and inhibits inflammatory responses dependent on NF-κB [144]. Prunetin was found to improve the lifespan of *Drosophila melanogaster* and increase the expression of the longevity-related gene *SIRT1*. Diet supplementation with prunetin increases the survival of adult flies by 3 days and improves climbing activity in males. It increases the expression of SIRT1 and AMPK and decreases glucose levels in male flies [145].

Formononetin

Formononetin is an isoflavonoid enriched in soy and some other leguminous plants. The antioxidative potential of formononetin is well known, and it reduces ROS generation [146]. It is also known to exert antihyperlipidemic and cardioprotective effects [147]. It is an important ingredient of one of the polyhedral formulations used for managing nephropathy [148]. Formononetin also possesses anti-inflammatory activities, mainly by inhibiting the release of HMGB1. It was found to upregulate SIRT1, which is responsible for reducing HMGB1 acetylation and its release [149]. It was also found to be protective against type 2 diabetes and improves insulin sensitivity, reduces hyperglycemia, and increases pancreatic SIRT1 expression in type 2 diabetic rats [150]. It is proposed to be a partial PPARγ agonist and provide protection against liver injury by upregulating SIRT1 and inactivating the JNK-dependent inflammatory pathway [148, 151]. A study by Oza and Kulkarni showed that formononetin was able to reduce oxidative stress in kidney cells of diabetic rats by increasing the SIRT1 expression [150].

Based on these studies, which show the role of phytoestrogens in stimulating SIRT1 expression, previous beneficial role of sirtuins in preventing kidney diseases, and recently reported role of phytoestrogens like formononetin in reducing the kidney damage by captivating SIRT1, it can be inferred that different naturally occurring phytoestrogens are potential compounds of biological origin to prevent the onset and prevention of various renal diseases (summarized in ▸ **Fig. 4**).

Authors Perspectives

Sirtuins, particularly SIRT1, which are NAD+-dependent deacetylases, regulate various metabolic processes that are critical in the context of kidney diseases, including inflammation and oxidative stress. The protective effects of phytoestrogens like genistein and resveratrol on renal health have been linked to their ability to activate SIRT1, leading to enhanced mitochondrial function and reduced oxidative damage. For instance, genistein has demonstrated a capacity to downregulate inflammatory cytokines and improve kidney function in diabetic models, suggesting its direct interaction with SIRT pathways to mitigate renal injury.

Despite these promising findings, it is essential to address the experimental framework in which phytoestrogens exert their effects. Factors such as dosage, duration of exposure, and the specific metabolic state of the organism can have profound influences on the outcomes. For instance, while lower doses of resveratrol have been shown to activate SIRT1 and provide protective effects, higher concentrations may induce adverse effects, such as increased oxidative stress and renal fibrosis. This dose-dependent response underscores the importance of optimizing therapeutic regimens to harness the beneficial effects of phytoestrogens while minimizing risks.

The bioavailability of phytoestrogens is another critical factor affecting their renal protective roles. Variability in absorption, metabolism, and individual gut microbiota can lead to substantial differences in the effective concentration of these compounds in the body. For instance, significant variation has been observed in the efficacy of soy isoflavones among individuals, mainly influenced by genetic and dietary factors. Therefore, while some studies report beneficial effects on renal function, others fail to demonstrate significant improvements, raising questions about the generalization of the findings [152].

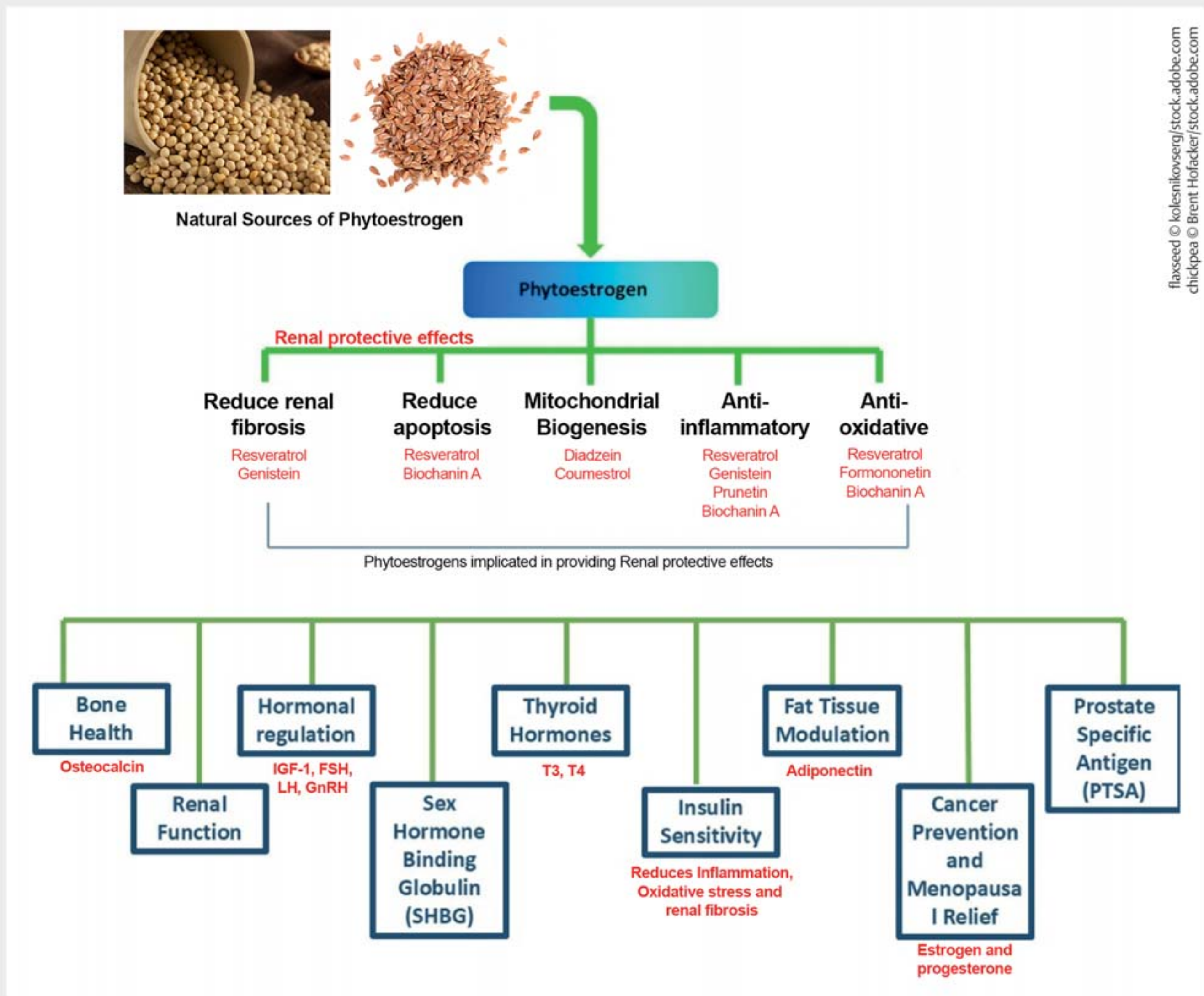
Furthermore, the hormonal milieu of the individual can modulate the effects of phytoestrogens. For example, in postmenopausal women, the estrogenic activity of phytoestrogens may provide additional renal health benefits, potentially due to their synergistic effects with endogenous hormones [153, 154]. However, in hormone-sensitive individuals or in younger populations, the effects may differ or lead to adverse outcomes.

While the potential benefits of phytoestrogens, including improved renal function and protection against CKD, are encouraging, they are counterbalanced by risks associated with endocrine disruption. Phytoestrogens can interfere with the hormonal balance, raising concerns about their safety, particularly in vulnerable populations. The dual nature of these compounds as both potential protectants and endocrine disruptors complicates their therapeutic use.

Moreover, the inconsistencies in the outcomes of the reported studies regarding the effectiveness of phytoestrogens for renal protection emphasizes the need for more rigorous clinical trials. Many studies lack standardization in methodology, including variations in dosages and the forms of phytoestrogens administered. Such discrepancies hinder the ability to draw definitive conclusions regarding their therapeutic potential.

Future Prospects

Phytoestrogens are a diverse group of compounds, including isoflavones, lignans, and coumestans, that have been shown to have estrogenic and antiestrogenic effects. These compounds are found in a variety of plant-based foods, such as soybeans, flaxseeds, chickpeas, and lentils. In recent years, there has been growing interest in the potential health benefits of phytoestrogens, particularly in the area of renal protection. Studies have shown that phytoestrogens can reduce oxidative stress and inflammation in the kidneys, which are two key factors in the development of renal disease. Clinical trials in humans have also shown promising results (▸ **Table 4**). A randomized controlled trial conducted in patients, and the findings, suggests that dasatinib plus quercetin reduced adipose tissue senescent cell burden [29]. In



► **Fig. 4** Phytoestrogens (PEs) have several health implications, particularly for renal health, through various mechanisms.
1. Bone Health and Renal Function: PEs affect osteocalcin (OTC) and other markers related to bone health, which can also impact overall renal function.
2. Hormonal Regulation: They influence levels of several key hormones: Growth Factor (IGF-1): By modulating IGF-1 levels, PEs can impact kidney function. Reproductive Hormones (FSH, LH, GnRH): Their effects on these hormones may influence hormonal balance and renal health.
3. Sex Hormone-Binding Globulin (SHBG): Alterations in SHBG levels by PEs could influence sex hormone availability and, consequently, renal health.
4. Thyroid Hormones (T3, T4): By affecting thyroid hormone levels, PEs might have implications for metabolic processes and renal health.
5. PEs enhance insulin sensitivity, which helps protect kidney function by reducing inflammation, oxidative stress, and fibrosis.
6. PEs modulate fat tissue by reducing adipogenesis, enhancing lipid metabolism, and upregulating adiponectin levels, leading to improved insulin sensitivity and metabolic health. These effects contribute to better weight management, reduced inflammation, and lower risks of diabetes and cardiovascular diseases.
7. PEs modulate estrogen and progesterone activity by binding to estrogen receptors and inhibiting enzymes like aromatase, leading to potential benefits like cancer prevention, improved bone health, and relief from menopausal symptoms. Their ability to act as both estrogen agonists and antagonists provides a balance of hormonal effects.
8. Prostate-Specific Antigen (PTSA): There may be indirect effects on renal health due to PEs' association with PTSA levels.

▶ **Table 4** Clinical experimentations on different phytoestrogens.

Phytoestrogen	Experimental model	Dosing	Outcome	Ref.
Genistein	Male Wistar rat	1 mg/kg per day	Genistein decreases glutathione (GSH) and increases lipid peroxides, hence improving the response to insulin and the performance of the kidneys.	[179]
	ICR mice (female)	0.025 %, 0.1 %	Taking 0.1 % genistein may help avoid kidney damage in diabetes patients with high FBG levels. Genistein is most effective in individuals with diabetes whose blood glucose levels are somewhat above normal.	[180]
	Female mice	160 mg/kg per day	Kidney damage is reduced by genistein, according to preclinical evidence.	[181]
Quercetin	Sprague-Dawley rats	20 mg/kg, IP	Quercetin's ability to operate as an antioxidant and scavenger of free radicals protects against oxidative organ damage caused by irradiation.	[182]
	Adult human	500 mg twice daily	Dasatinib and quercetin functioned together to reduce the number of aged cells found within fat tissue, as expression of p16INK4A and p21CIP1, the activity of senescence-associated β-galactosidase, and the number of adipocyte progenitors with impaired proliferative capacity. Macrophages in adipose tissue were reduced.	[183]
Resveratrol	Male Wistar rats	5 mg/kg body weight for 16 weeks	Reduced kidney cell apoptosis and NF-κB function.	[184]
		20 mg/kg for 8 days	Reduction in protein loss in the urine, renal hypertrophy, and mesangial matrix expansion along with mesangial cell hyperplasia.	[185]
		8 mg/kg for 8 days	Minimize the effects of oxidative stress and the number of dead renal tubular epithelial cells.	[186]
	Sprague-Dawley rats	20 mg per kg body weight (daily) for 7 days	Decreased the damage to the renal interstitial. Tubular atrophy and dilation are diminished along with collagen rupture reduction. Resveratrol inhibits EMT and fibrosis *in vivo* and *in vitro* by antagonizing the hedgehog pathway, benefiting fibrotic kidney disease patients.	[187]
	T2DM patients	10 mg per day for 4 weeks	1. Resveratrol consumption reduced oxidative stress, which in turn makes insulin signaling through the Akt pathway more effective. 2. Renal filtering rate has increased along with insulin sensitivity where the glucose level was decreased along with creatinine.	[188]
Naringenin	Rat	50 or 100 mg/kg	Protected kidney function.	[189]
	Sprague-Dawley rats	100 or 200 mg/kg	In a rat model of renovascular hypertension, naringenin reduced kidney damage by correcting an abnormality in renin-angiotensin system stimulation.	[190]
Daidzein	Chinese women	63 mg	Improve signs of kidney health along with markers.	[191]
	OVX rats	1 mg/kg	Daidzein ameliorated glomerulosclerosis, stress-induced oxidative damage, and inflammation in UUO-OVX rats through cooperation with AT1R and MasRs. In order to protect older women's kidneys from the effects of menopause, daidzein may be used as an estrogen replacement medication.	[192]
Coumestrol:	Pregnant ICR mice	200 µg/kg	Newborn mice may have their renal calcium metabolism altered if coumestrol is given to their mothers during pregnancy and breastfeeding.	[193]

continued next page

▸ **Table 4** *Continued*

Phytoestrogen	Experimental model	Dosing	Outcome	Ref.
Prunetin	Molecular docking	NA	Medication candidate for diabetic nephropathy.	[194]
	RT-4 cells	21.11 and 42.22 µg/mL	By activating the CASP3 and TNF-α genes, prunetin suppresses nitric oxide production and induces cell death in urinary bladder cancer.	[195]
Formononetin	Male db/db mice	25 mg/kg and 50 mg/kg	Reduced oxidative damage in diabetic neuropathy; inhibited renal fibrosis progression by upregulating Sirt1 expression and activating the Nrf2/ARE signaling pathway.	[196]
	db/db mice	25 or 50 mg/kg/day for 8 weeks	Renal function was protected, oxidative stress was decreased, and glucose homeostasis was significantly enhanced. The expression of Smad3 and a similar extracellular matrix deposition regulating factor was also dramatically downregulated at the protein and mRNA levels. Formononetin has a significant renoprotective impact in diabetic neuropathy, which also showed anti-fibrosis action by reducing Smad3 expression.	[197]
	C57BL/6 mice	40 mg/kg/day	Lowered the expression of profibrotic genes like α-SMA, Col1a1, and fibronectin, and improved tubular injury.	[198]
	Male Wistar rats	75 mg/kg	Activation of the PPAR/Nrf2/HO1/NQO1 pathway provides protection against cisplatin's induction of acute renal damage.	[199]
	Male Wistar rats	15, 50, 75 mg/kg	Formononetin inhibited p53 expression by increasing the levels of MDM2 and MDMX. Formononetin protected against cisplatin-induced acute kidney damage by increasing the number of tubular cells in the kidney and reducing apoptosis.	[200]
	Rat	75 mg/kg	Formononetin's Nrf2-mediated apoptosis inhibition protected the kidneys, and formononetin increased BCL-XL and BCL-2 expression by inhibiting BAX, cytochrome c, caspase-9, and caspase-3.	[201]
	Male Wistar rats	40 mg/kg	Enhanced antioxidants and decreased oxidative stress, proinflammatory mediators, and apoptosis; formononetin protected kidneys from damage.	[202]
	Male Wistar rats	60 mg/kg for 2 weeks	Boosts Nrf2 signaling and prevents kidney damage by acting as an antioxidant, anti-inflammatory, and antiapoptotic.	[203]

addition to their antioxidant and anti-inflammatory properties, phytoestrogens have also been shown to have other beneficial effects on the kidneys. For example, they can improve vascular function and reduce blood pressure, both of which are important factors in the development of renal disease [155].

Despite these promising findings, there is still much to learn about the potential role of phytoestrogens in renal protection. More research is needed to determine optimal dosages, formulations, and treatment duration, as well as to identify which types of phytoestrogens are most effective. Additionally, more studies are needed to determine whether phytoestrogens are effective in preventing renal disease, or if they are only useful as a treatment for existing renal disease.

Conclusion

Evidence suggests that a phytoestrogen-rich diet is beneficial in slowing down the progression and development of renal diseases. Multiple studies conducted in both humans as well as animals have demonstrated that a soy- and flaxseed-containing diet improves chronic renal diseases. Several mechanisms have been proposed for this, like antioxidative actions, modulation of TGF-β1, decreasing apoptosis, decreasing renal fibrosis, and cytokine activation. However, studies have also reported the adverse health effects of phytoestrogens, and they are categorized as endocrine disruptors, being able to increase the risk of infertility and cancer in estrogen-sensitive organs. The observance has, however, only been made in animals, *in vitro*, and epidemiological studies, whereas clinical studies mostly report the absence of these adverse effects, except for some gastrointestinal disturbances. These studies are mostly either observational or of short duration involving a lesser number of patients. This warrants the need to conduct long-term perspectives of randomized clinical trials for observing the effect of dietary phytoestrogens on the progression of chronic renal diseases.

Sirtuins, particularly SIRT1, are the key regulators of energy metabolism in cells. Except for their primary role as histone deacetylases, they also exhibit deacetylation of various cellular regulatory proteins like NF-κB p65 subunit, FOXO1, p53, and STAT. Sirtuins have been able to provide renal protection by improving mitochondrial biogenesis and reducing ROS in kidneys. Mitochondrial biogenesis helps to improve fatty acid oxidation, ameliorating hypoxia and age-related renal injury, thus helping in renal protection. The reduction of ROS helps in mitigating diabetic glomerular injury and nephrotoxicity. Recent studies have shown that phytoestrogens such as formononetin, genistein, daidzein, resveratrol, and coumestrol can activate sirtuins and play an important role in mitochondrial biogenesis and ROS reduction. These studies corroborate that phytoestrogens can play an important role in preventing and treating renal diseases by modulating the expression of sirtuins. Further studies are required to conclusively determine the mechanism, the type of sirtuin activated by phytoestrogens, and the safety of phytoestrogens (considering their role as endocrine disruptors) as renal protective agents.

Contributors' Statement

Debojyoti Mandal: Conceptualization, Methodology, Software, Writing- Original draft preparation, Visualization, Investigation. Nahid Akhtar: Data curation, Writing- Original draft preparation. Sana Shafi: Writing-Reviewing and Editing. Jeena Gupta: Supervision, Validation, Writing-Reviewing and Editing.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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