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The role of NADPH oxidase in diabetic kidney disease: Mechanisms, isoforms, and therapeutic opportunities

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ABSTRACT

Diabetic kidney disease (DKD) is a long-term complication of diabetes mellitus that significantly contributes to morbidity and mortality. In the multifactorial pathogenesis of DKD, NADPH oxidase (Nox) has recently been identified as a pivotal player in both the initiation and progression of disease. Nox enzymes are key producers of reactive oxygen species, perpetuating oxidative stress, which serves as a major trigger for renal cell injury. Thus, it is imperative to assess the precise role of Nox-mediated oxidative stress and the distinct Nox isoforms involved in DKD. Our review provides insights into the intricate mechanisms through which Nox and its subtypes contribute to the pathogenesis of DKD, emphasizing its involvement in glomerular (podocyte, mesangial, and endothelial) and tubular injury, as well as subsequent interstitial inflammation and fibrosis. In addition, we have summarized emerging therapeutic strategies targeting Nox inhibition to mitigate the progression of DKD, which offer focused clinical interventions for improved patient outcomes.

1. INTRODUCTION

Diabetic kidney disease (DKD) is a major microvascular complication of diabetes, leading to end-stage kidney disease [1]. The prevalence rate varies across the world, ranging from 27% to 50%. In addition, DKD significantly contributes to cardiovascular morbidity and mortality and reduces the health-related quality of life of affected individuals [1]. DKD has emerged as a major global public health and economic challenge, with the impact being particularly severe in less developed countries. Therefore, a substantial unmet medical need persists, underscoring the urgency of pursuing novel therapeutic targets [2].

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DKD is a progressive disease caused by hyperglycemia and hemodynamic changes, and its pathophysiology is considered complex, affecting almost all nephron structures, including renal tubular epithelia, glomerular endothelia and epithelia, podocytes, and the mesangial matrix. These alterations ultimately result in albuminuria, progressive loss of kidney function, renal fibrosis, and inflammation, with oxidative stress serving as a central mechanism linking hyperglycemia to DKD progression [3]. Oxidative stress arises from the activation of the polyol pathway, and the accumulation of advanced glycation end products stimulates the production of multiple cytokines, which collectively injure the renal microvasculature and exacerbate kidney damage. Zhang *et al.* [4] reported that the levels of the oxidative marker 8-hydroxy-deoxyguanosine were significantly elevated in DKD patients and progressively increased with worsening proteinuria [4]. Studies suggest that oxidative stress plays a pivotal role among the myriad of factors contributing to

DKD pathogenesis, serving as a common denominator in orchestrating renal damage, including accumulation of the extracellular matrix, tubular and glomerular cell hypertrophy, and the consequent development of proteinuria [5,6]. Recently, Petrovic *et al.* [7] demonstrated that selonsertib reduces GFR decline by directly inhibiting MAP3K5, a key mediator of oxidative stress signaling [7]. Similarly, in a triple-blind, placebo-controlled trial, Jaafarinia *et al.* [8] reported that antioxidant supplementation lowered the levels of oxidative stress-induced inflammatory markers. Zitouni *et al.* [9] reported that in early DKD, antioxidant therapy enhances renal blood flow and is associated with improved eGFR.

Oxidative stress is characterized by the upregulation of reactive oxygen species (ROS) production alongside the concurrent depletion of antioxidative mechanisms. When the level of ROS exceeds inherent antioxidative defenses, it induces the oxidation of diverse tissue biomolecules, including DNA, proteins, carbohydrates, and lipids. ROS include molecular oxygen and its derivatives, such as superoxide anion (O2−), hydroxyl radical (HO), hydrogen peroxide (H2O2), peroxynitrite, hypochlorous acid, nitric oxide (NO), and lipid radicals [10,11]. ROS generation can occur through various pathways, such as mitochondrial oxidative phosphorylation, xanthine oxidase, or uncoupled nitric oxide synthase and NADPH oxidases (Nox). Among these mechanisms, Nox-induced ROS production has emerged as the primary contributor to intrarenal oxidative stress. The widespread renal distribution and ability to produce ROS establish Nox as a significant contributor to DKD, triggering substantial damage to glomerular and tubular cells and subsequently leading to interstitial inflammation and fibrosis. Insights into the broader implications of Nox-mediated renal injury can provide a comprehensive understanding of disease pathology and potential therapeutic interventions [12]. In the present review, we focus on the current perspective and evidence on the mechanism by which Nox contributes to DKD pathogenesis, including other microvascular and macrovascular complications. This review systematically integrates existing knowledge on the role of individual Nox isoforms in glomerular, tubular, and inflammatory injury in DKD onset and progression. In addition, the review bridges preclinical mechanistic evidence with emerging therapeutic data on NOX inhibitors.

2. NAPDH OXIDASE

NADPH oxidase is a multicomponent enzyme that facilitates the transfer of electrons from NADPH to molecular oxygen, a process catalyzed by the Nox catalytic subunit, resulting in ROS generation [13]. Early studies revealed that phagocytic NADPH oxidase is composed of Nox2 (also known as $gp91^{phox}$). Homologs of this enzyme have subsequently been identified in nonphagocytic cells, including renal cells; heart, lung, and carotid body cells; and vascular smooth muscle cells (VSMCs) [14,15]. In recent years, significant attention has been given to Nox in the kidney, and studies on homogenates of rabbit kidneys indicate that the primary source of ROS generation in the renal cortex and outer medulla is Nox [16].

To date, the Nox family comprises five Nox family members (Table 1), namely, Nox1, Nox2 (gp91phox), Nox3, Nox4, and Nox5, and two dual oxidase family members, namely, Duox1 and Duox2 [17]. Nox1-3 is composed of two membrane-bound components, namely, Nox subunits and P22phox. The activation of this enzyme requires cytosolic components, which include NOXO (nox organizer 1), NOXA1 (Nox activator 1), P67phox, P40phox, P47phox, and Rac1/2. The regulation of Nox5 and Duox1/2 involves a calcium-binding EF-hand motif, and functionality depends upon the intracellular calcium concentration, whereas Nox4 does not require a cytosolic part for activation [18,19].

2.1. NAPDH oxidase in the kidney

NADPH oxidase subunits are widely distributed throughout the kidney, including in blood vessels, interstitial cells, glomeruli, and tubules. Spectroscopic analysis of human mesangial cells [20] and reverse transcribed-polymerase chain reaction of human podocytes revealed the expression of Nox2, P67phox, P22phox, and P47phox [21]. The renal cortex produces Nox1 and Nox2. The outer medullary thick ascending limb of the loop of Henle expresses Nox2.

Nox-4 is the prevailing isoform of NADPH oxidase expressed within the kidney epithelium, and its distribution extends to key structures such as the vasculature, glomeruli, mesangial cells, and various nephron segments [22]. It was initially identified in the kidney, so this enzyme was named Renox or kidney oxidase [22]. Akira *et al.* conducted a study employing immunohistochemical methods to examine the localization of Nox4 in the human kidney. Their observations revealed significant levels of the Nox4 protein in distal tubular cells within the human renal cortex, with a notable concentration in the vicinity of erythropoietin-producing cells [23]. The calcium-sensitive isoform Nox5 is also present in the human kidney and vasculature; however, the absence of this enzyme in rodents has made exploring its role in renal pathologies more challenging [24]. Moreover, there are currently no available data regarding the expression of Nox3 or Duox1/2 in the kidney.

2.2. Role of Nox in diabetic kidney disease pathogenesis

Multiple pathways lead to ROS production, but recent studies have indicated that Nox produces ROS in many nonphagocytic cells, including renal cells, and is thought to contribute significantly to DKD pathogenesis. Under healthy conditions, cells tightly control the production and removal of ROS. This balance ensures that a controlled level of ROS remains, which acts as a secondary messenger in signaling pathways within cells, coordinating various biological processes. However, in pathological conditions, including DKD, Nox isozymes and their regulating proteins are overexpressed, leading to the uncontrolled generation of ROS. This disruption in the balance of ROS homeostasis results in a gradual increase in ROS levels and oxidative renal damage [12]. Numerous *in vivo* and *in vitro* studies have proven the significant role of Nox-dependent ROS in the development of glomerular injury, including the accumulation of ECM proteins, early mesangial cell hypertrophy, mesangial expansion, glomerulosclerosis, endothelial dysfunction, podocyte apoptosis, and disruption of glomerular hemodynamics in DKD (Fig. 1) [8,12].

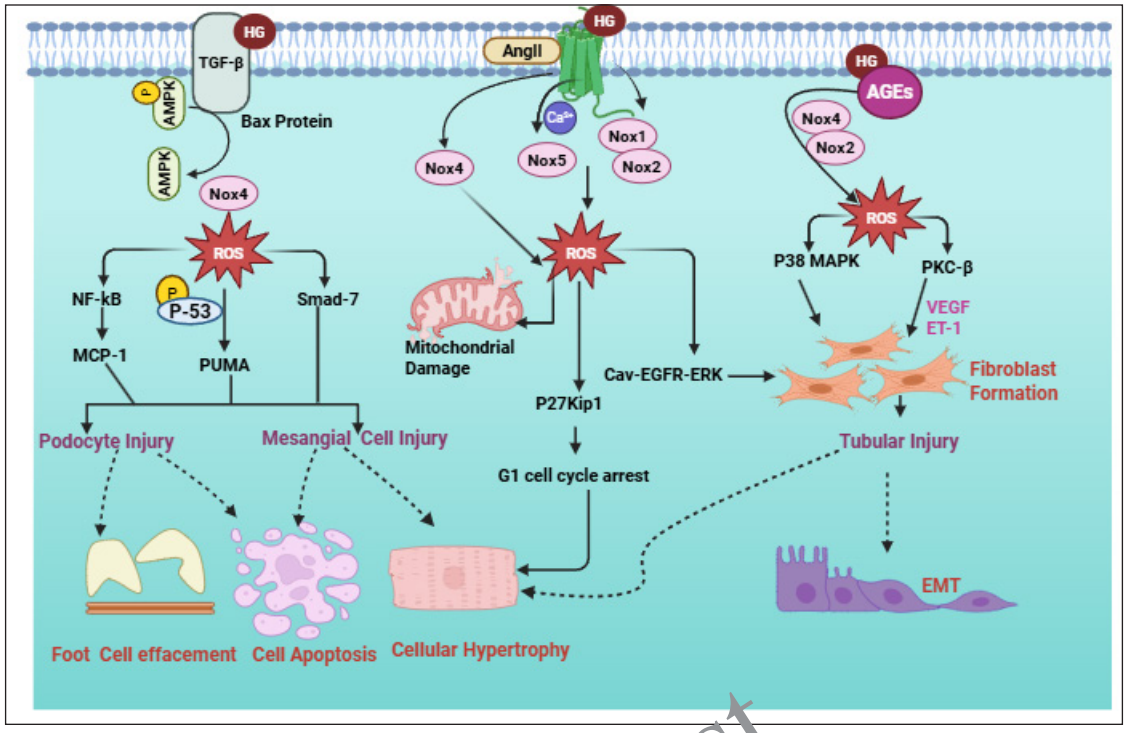

Figure 1. NADPH oxidase-mediated renal injury in DKD.

Ang II: Angiotensin II; HG: Hyperglycemia; TGF-β: Transforming growth factor-β; Ca2+: Calcium ions; RO: Reactive oxygen species; PCNA: Proliferative cell nuclear antigen; VCAM-1: Vascular cell adhesion molecule-1; MCP-1: Monocyte chemoattractant protein-1; PUMA: p-53 upregulated modulator of apoptosis; EMT: Epithelial–mesanchial cell transition.

2.3. Nox in glomerular injury

2.3.1. Endothelial cell injury

Nox plays a significant role in generating ROS within endothelial cells, and its activation is induced by various stimuli, such as vascular endothelial growth factor (VEGF), cytokines, shear stress, hypoxia, angiopoietin-1, and angiotensin II (AngII) [25]. These stimuli initiate the activation of several downstream signaling pathways, including mitogen-activated protein kinases (MAPKs), Akt, and endothelial nitric oxide synthase (eNOS), which are crucial for endothelial cell migration and proliferation [26]. Consequently, it enhances ROS production by triggering Rac1-dependent activation of Noxs (Nox1, Nox2, and Nox4) in endothelial cells [27].

In the Ang II-dependent Nox pathway, eNOS serves as the primary source of endothelial cell injury. Under hyperglycemic conditions, exposure of glomerular endothelial cells to Ang II leads to increased expression of cyclooxygenase 2 and eNOS uncoupling [28]. The NO produced from the uncoupling reaction forms peroxynitrite, which subsequently reacts with tyrosine and other proteins, ultimately generating cytotoxic nitrotyrosine, which damages endothelial cells [29].

The intricate role of Nox isoforms has been studied extensively. In *in vivo* studies in mouse models, an upstream role of Nox1, Nox2, and Nox4 has been revealed by RNA interference in mediating the diabetic uncoupling of eNOS, resulting in subsequent impairment of endothelial function [30–32]. However, a recent study by Augusto *et al.* introduced a novel perspective by elucidating a mechanism involving Nox5-regulated vascular function. This study involved the exposure of cultured human endothelial cells to Ang II and endothelin-1 (ET-1) in the presence of calcium and revealed that the activation of Nox5 was triggered by Ang II and ET-1, resulting in the generation of ROS and the stimulation of proliferating cell nuclear antigen and vascular cell adhesion molecule-1 via ERK1/2 phosphorylation, which contribute to cellular hypertrophy and endothelial inflammation [33].

2.3.2. Mesangial cells

In mesangial cell hypertrophy, Nox-dependent ROS act as secondary messengers of Ang II and arachidonic acid to stimulate the serine–threonine protein kinase Akt/PKB for protein synthesis in mesangial cells [12]. In support of this hypothesis, Gorin *et al.* [34] reported increased generation of Nox4-mediated ROS in cultured diabetic mesangial cells compared with control cells. In addition, they noted elevated levels of the extracellular matrix protein fibronectin, along with increased activity of Akt/protein kinase B and ERK1/2 [34]. Another *in vitro* study revealed high levels of Nox4 transcripts in rat glomerular mesangial cell cultures via northern blot analysis [35]. In a mouse model of DKD, the deletion of Nox4, but not Nox1, led to protection against glomerular injury, which was evident from reduced levels of albuminuria, preserved structural integrity, and decreased accumulation of extracellular matrix proteins [36]. In contrast, Nox1 was found to play a significant role in mesangial fibrogenesis when mesangial cells

were treated with high glucose plus AGE for 48 hours, resulting in elevated levels of fibronectin, TGF-beta, and superoxide. In addition, hypertrophy was suppressed in cells lacking Nox1 but not in cells lacking Nox2 or Nox4 [37]. Fibrogenesis mediated by ROS derived from Nox1 occurs through inducible nitric oxide synthase (iNOS) [19].

Recent studies have demonstrated the induction of mitochondrial ROS in mesangial cells, followed by the translocation of PKC isoforms from the membrane to the cytosol. These isoforms are activated by Nox, notably Nox4. Within this context, PKC-α has been identified as a key player, as it induces the expression of nephrin and VEGF, ultimately contributing to the development of albuminuria. On the other hand, the second form, Protein kinase C-β (PKC-β), promotes matrix accumulation through the upregulation of TGF-β levels and increased protein synthesis [38]. Supporting findings were reported in a model of streptozotocin-induced diabetes by Thallas *et al.* [39] who demonstrated that the renoprotective effects of broad deletion of Nox4 resulted in a significant reduction in albuminuria and glomerular sclerosis as well as decreased levels of mitochondrial and cytosolic sources of superoxide. Furthermore, the expression of PKC-α and -β isoforms, fibronectin, and glomerular collagen IV is reduced [39]. *In vitro* studies have revealed another mechanism involving the association of microRNAs, which act as effectors of TGF-β, with Nox4 in mesangial cell injury. Specifically, the 3′-untranslated region of NOX4 serves as the target site for miR-25 in DKD, thereby regulating its expression [40].

2.3.3. Podocyte

Podocyte apoptosis, which is observed early in DKD, leads to the gradual loss of these cells in the glomeruli, resulting in the excretion of albumin in the urine. Both *in vivo* and *in vitro* studies have revealed that elevated levels of Nox-mediated ROS trigger podocyte apoptosis [41]. The molecular mechanism associated with ROS-induced podocyte apoptosis involves apoptosis signal-regulating kinase 1 (ASK1) [39]. The stimulation of ASK1 by the stress response activates both the MKK4/MKK7-JNK pathway and the MKK3/MKK6-p38 kinase pathway via TGF-β1 [42]. TGF-β induces the expression of the Bax protein, which in turn triggers the release of cytochrome C from the mitochondria. This release leads to the activation of the effector caspase-3, initiating the apoptotic pathway. Notably, the deactivation of AMP-activated protein kinase results in increased expression of NOx, which in turn promotes apoptosis by inducing the phosphorylation of p53. This phosphorylation event subsequently activates factors such as p53-upregulated modulator of apoptosis (PUMA) [43]. In addition, a collaborative effect of Smad7 involves the inhibition of the nuclear translocation and transcriptional activity of the cell survival factor NF-κB, thereby enhancing apoptosis [44]. Corroborating evidence has been reported in ASK1-/-mouse embryonic fibroblasts exposed to H_2O_2, which exhibit a lack of sustained JNK and p38 kinase activity and resist oxidative stress-induced apoptosis [46]. An *in vitro* study with cultured mouse podocytes exposed to high glucose revealed the sequential regulation of Nox oxidases by cytochrome P450 of the 4A family in podocyte injury, which mediates the stimulatory impact of high glucose on the expression of Nox4 and Nox1 in podocytes, leading to increased production of ROS [46].

Ang II and TGF-β, which are produced by either mesangial or podocytes, can harm both cell types through autocrine/paracrine Nox activation. This highlights the complex interplay between these cells in diabetes, suggesting that Nox enzymes are key players in damaging reciprocal interactions [47].

Jha *et al.* [36] reported that Nox4 mRNA levels increased when podocytes were exposed to a high-glucose environment. Furthermore, the introduction of TGF-β into this hyperglycemic context exacerbated the upregulation of Nox4 gene expression. In addition, there was a minor increase in Nox5 expression, although no significant changes in Nox1 or Nox2 expression were detected. The potential role of Nox4 was further demonstrated in a mouse model of DKD in which the deletion of Nox4, but not Nox1, reversed podocyte injury [36]. However, a recent study in which the antioxidant probucol was administered revealed decreased albuminuria, decreased accumulation of the ECM protein collagen IV, and alleviation of podocyte damage through the inhibition of Nox2 expression [12]. Nox4-dependent activation of PUMA for podocyte apoptosis and foot cell effacement was detected in the OVE26 model of diabetic mice [42].

Although the evidence supporting the involvement of Nox4 in podocyte injury and apoptosis linked to albuminuria in diabetes is well established, increasing attention has been given to the role of Nox5 in podocyte dysfunction. Recently, Holterman *et al.* [47] developed a transgenic mouse model expressing human Nox5, as rodents naturally lack this enzyme, and observed podocyte foot effacement and albuminuria in a Nox5 knockout model via siRNA-inhibited AngII–induced production of ROS and induced changes in podocyte cytoskeletal dynamics. This evidence suggests that Ang II triggers the generation of ROS in human podocytes through a mechanism dependent on Nox5. This process appears to be facilitated by the Ang II-induced elevation of intracellular calcium levels, which in turn activates renal Nox5. A human renal biopsy study confirmed earlier findings, showing that Nox5 was specifically present in diabetic but not in nondiabetic glomeruli [48].

In summary, both Nox4 and Nox5 are pivotal in ROS-induced glomerular injury, but investigations of other Nox subunits are scarce. However, conflicting results have been reported regarding the involvement of Nox1 in this context. In endothelial cells, mesangial cells, and podocytes, the reciprocal crosstalk mediated by Ang II and TGF-β drives oxidative injury via NOX activation. The convergence of pathways, including eNOS uncoupling in endothelial cells, PKC/TGF-β signaling in mesangial cells, and apoptotic cascades in podocytes, points to a broader network in which NOX isoforms act in a paracrine manner [46].

2.4. Nox in tubular injury

Diabetes not only impairs glomerular cells but also has detrimental effects on renal tubular cells. Podocyte injury, which contributes to the onset of glomerulosclerosis and proteinuria, together with the development of tubulointerstitial fibrosis, represents a critical sequence of events driving the progression

Table 1. Expression of Nox isoforms in the kidney.

Isoforms	Amino acids present	Cytosolic subunits	Catalytic subunits	Site
Nox1 [25]	290–564	NoxA1,NoxO1,P47phox	Nox1	Smooth muscle cells of renal endothelium(afferent and efferent arteriole)
		Rac1/2	P22phox	Mesangial cells
				Proximal tubular cells, podocyte
Nox2 [26]	290–570	P67phox, P47phox, P40phox,Rac1/2	Nox2	Smooth muscle cells of renal endothelium
			P22phox	Glomerular epithelial cells
				Mesangium
				Podocyte
				TAL
				Distal convoluted tubules
Nox3 [26]	288–568	NoxO1, NoxA1, Rac1/2	Nox3	-
			P22phox	
Nox4 [23]	304–538	Does not require a cytosolic regulator to function	Nox4	Mesangium, Podocyte
			P22phox	Glomerular epithelial cells
				proximal convoluted tubular cells,
				renal vasculature,
				TAL,
				Macular densa,
				cortical and medullary collecting tubules
Nox5 [24]	413–737	Calcium binding EF-motif	Nox5	Smooth muscle cells of renal endothelium(afferent and efferent arteriole), Podocyte
				Glomerular epithelial cells

Nox: NADPH oxidase; NOXO: Nox organizer 1; NOXA1: Nox activator 1; TAL: Thick ascending limb of Henle.

of DKD. Like glomerular injury, Nox-derived ROS play a significant role in tubular damage [34]. Overproduction of ROS triggered by hyperglycemia, coupled with Ang II-mediated TGF-β production, plays an active role in causing dysfunction in tubular and interstitial cells, which is characterized by interstitial fibroblasts and excessive deposition of the extracellular matrix within the tubulointerstitial space, ultimately disrupting tubular reabsorption. PKC-β appears to serve as a potential upstream regulator of Nox4 expression in tubules, thereby amplifying VEGF and ET-1 expression, culminating in tubulointerstitial injury [49]. Moreover, in mouse proximal tubule culture, activation of p38MAP kinase and upregulation of TGF-β1/2 and fibronectin are noted, attributed to ROS generation mediated by Nox2 and Nox4 [50].

Extensive studies have shown that Ang II utilizes Nox4 as a mediator of its injurious effects on tubular epithelial cells. Ang II stimulates Src-dependent phosphorylation of caveolin-1 (Cav) and epidermal growth factor receptor (EGFR). This prolonged Cav-EGFR-ERK signaling pathway induces dedifferentiation via epithelial–mesenchymal transition [51]. Furthermore, Ang II-mediated Nox4 plays a role in mitochondrial dysfunction and apoptosis in proximal tubular injury [52]. Following binding to AT1 receptors, Ang II upregulates p22phox expression, potentially activating the Nox enzyme. This triggers the formation of ROS, leading to increased expression of p27Kip1, which is a G1-phase cyclin/cyclin-dependent kinase complex. Subsequently, p27Kip1 induces G1-phase arrest, ultimately resulting in cellular hypertrophy [52]. Nox acts as a mediator of insulin-like growth factor I, which induces the expression of extracellular matrix proteins in tubular cells via Akt phosphorylation. This finding was confirmed by David et al in an *in vitro* study in which proximal tubular cells were infected with an adenovirus carrying wild-type Nox4. Compared with the control construct, this construct, Ad-Nox4, increased Nox4 expression and fibronectin expression [53].

Nox-derived ROS are suggested to contribute to dysfunction in tubular reabsorption. Patrik *et al.* revealed that excessive exposure to Nox-derived ROS leads to increased transport-dependent oxygen consumption and elevated tubular sodium (Na+) transport by altering Na+/H+ exchanger isoform 3 activity. This contributes to a subsequent decrease in cortical and medullary oxygen tension [54]. Furthermore, Ang II-mediated activation of Noxs, particularly Nox4, regulates the activity of sodium–glucose cotransporter 2 (SGLT2).

Numerous studies have confirmed the role of Nox4 in the generation of ROS within the tubular compartment. In both ApoE KO and C57/BL6 diabetic mice, the deletion of Nox4 led to a notable reduction in ROS levels within the kidney's tubular cells, but the deletion of Nox1 did not yield similar effects [39]. In proximal tubule culture, Nox4 was shown to

activate profibrotic processes through Nox4-sensitive p38 MAPK-dependent pathways [50]. In mouse proximal tubular cells exposed to high glucose, increased ADAM17 expression and activity, along with upregulated Nox4, were observed. Inhibiting ADAM17 resulted in reduced ROS production and fibrosis in diabetic OVE26 mice by downregulating Nox4, indicating a role for ADAM17 in Nox4-mediated tubular injury [55]. A recent study by He *et al.* revealed that high glucose-induced EMT is mitigated by reducing intracellular ROS levels through the downregulation of Nox1 and Nox4 but not Nox2 [56]. Similarly, Nox2 knockout mice do not exhibit a reduction in tubulointerstitial injury in insulin-deficient diabetes.

In the context of tubular injury, various Nox isoforms, notably Nox4 and Nox1, are implicated. Research on Nox2 is relatively limited, with indications that it is not linked to tubular dysfunction.

2.5. Nox in immune dysregulation

Tissue macrophages are the major immune cells strongly linked with interstitial fibrosis and the progression of DKD in the form of increasing levels of serum creatinine. In the early stages of DKD, M1 macrophages, which are proinflammatory in nature, infiltrate the renal parenchyma. After activation, M1 macrophages produce ROS and proinflammatory cytokines, leading to renal inflammation. However, as the disease progresses, M1 macrophages transform into the M2 phenotype, which is profibrotic in nature, resulting in a progressive decline in renal function [57].

Neutrophils constitute another major immune cell group that plays a key role in renal inflammation in DKD. Jaaban *et al.* [55] reported a significant correlation between the neutrophil–lymphocyte ratio and both DKD and albuminuria in patients with T2DM. The ROS produced by NOX are key molecules in the formation of neutrophil extracellular traps (NETs) [58]. NETs promote NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome activation, which in turn results in the release of proinflammatory cytokines, causing glomerular endothelial dysfunction, a hallmark of DKD [59].

Mast cells, which are rarely observed in normal kidney biopsies, are frequently noted in renal fibrosis due to various causes, including DKD. Mast cell degranulation releases many chemical mediators of inflammation, which play key roles in renal fibrosis in DKD [60].

Increased density of CD4+ (Helper T cells), CD8+ (Cytotoxic T cells), and CD20+ (B cells) cells in renal biopsies from patients with T2DM. Metabolic reprogramming in the form of a switch from oxidative phosphorylation to glycolysis as the primary source of energy is pivotal in T-cell activation. This switch results in elevated levels of NOX, leading to T-cell hyporesponsiveness, apoptosis, and activation. Dysregulation of the Th17 response and regulatory T cells is another important mechanism that results in the progression of DKD [61].

2.6. Nox in renal inflammation

Excessive ROS production leads to the production of proinflammatory cytokines, chemokines, and profibrotic factors in renal cells. The signaling pathways implicated in ROS-dependent renal inflammation include the transcription factor EGR-1, protein kinases PKC-α and PKC-ε, MAPK (ERK1/2), and the metabolically sensitive gene TXNIP. Multiple *in vivo* and *in vitro* studies have provided supporting evidence for this mechanism. In the Nox5 transgenic Akita mouse model, elevated levels of Nox5 correlate with increased expression of monocyte chemoattractant protein-1 (MCP-1), NF-κB, and toll-like receptor-4 (TLR4) in endothelial cells, VSMCs, and mesangial cells, which are linked to renal inflammation, compared with those in nondiabetic mice. Furthermore, the silencing of Nox5 in human renal cells resulted in a significant reduction in the increased expression of TLR-4 and MCP-1 induced by elevated glucose concentrations [62]. Similarly, studies have reported the role of Nox4 in ROS-mediated renal inflammation. Nox4 knockout in diabetic mice led to alleviation of renal expression of TLR-4 and MCP-1, along with reduced deposition of CD68+ macrophages in the glomeruli, and the levels of markers of M1 macrophages, including Cd80 and TNF-α, were also reduced [63]. In addition, EGR-1 was found to be a key modulator of Nox4, and the deletion of both Nox4 and Nox5 resulted in reduced albuminuria via the inhibition of Nox-mediated PKC-α [33]. In contrast to these findings, even in the absence of Nox4, these proinflammatory pathways are activated by Nox5 [64].

This evidence provides insight into the pivotal role of Nox enzymes in triggering the release of key proinflammatory pathways in DKD. Specifically, Nox4 and Nox5 have emerged as significant contributors to orchestrating renal inflammation.

2.7. Other sources of ROS—mitochondria

Mitochondria are a major source of ROS in diabetic kidney disease, and mitochondrial dysfunction amplifies renal injury through multiple mechanisms. In podocytes, impaired mitochondrial DNA repair, defective fatty acid oxidation, and excessive ROS generation contribute to apoptosis and glomerulosclerosis [65]. The electron transport chain (ETC) resides in the inner mitochondrial membrane, where respiratory complexes I–IV facilitate oxidative phosphorylation. Electron leakage from the ETC produces superoxide, which is subsequently converted to H2O2 by manganese superoxide dismutase in the mitochondrial matrix [66] Complexes I and III are considered the primary sites of ROS generation, and in hyperglycemic kidney tissue, their expression is often reduced. This impairment disrupts electron flow, promoting leakage and excessive ROS production under diabetic conditions [67].

Hyperglycemia-induced upregulation of NOX4 can further aggravate mitochondrial damage, highlighting the vulnerability of these cells. Similarly, renal tubular cells, which rely heavily on mitochondrial oxidative phosphorylation, are highly sensitive to ROS-driven injury. Mitochondrial dysfunction in tubular cells leads to depolarization of the mitochondrial membrane, opening of the permeability transition pore, and activation of apoptotic pathways [68]. Protective pathways, including α-Klotho–mediated NAD+ preservation, MRPL12–Nrf2 regulation of OXPHOS, and suppression of mineralocorticoid receptor signaling, counteract these effects. In addition, hypoxia-driven shifts toward anaerobic metabolism and lactate dehydrogenase-mediated ROS production exacerbate tubulointerstitial fibrosis. Novel strategies, such as

the use of activated protein C, have shown promise in reducing mitochondrial ROS while attenuating NLRP3 inflammasome activation [69].

2.8. Nox in diabetic retinopathy (microvascular complication)

Recent research has indicated that oxidative stress stimulated by elevated glucose levels is a key contributor to the microvascular complications observed in diabetic retinopathy. Nox-derived ROS contribute to diabetic retinopathy by inducing oxidative injury or acting as signaling molecules to regulate cellular activities such as proliferation, migration, and differentiation [64].

Nox2 contributes significantly to pathogenesis by promoting premature senescence of retinal endothelial cells, increasing retinal apoptotic factor levels, and increasing retinal hyperpermeability [70]. In 1998, Ellis *et al.* [68]] were the first to report increased Nox activity and endothelial cell dysfunction in the retina of diabetic rats compared with controls [71]. Subsequently, Nox2 was found to mediate the AGE-induced reduction in pigment epithelium-derived factors, which can further contribute to proliferative diabetic retinopathy [72]. The role of Nox4 was elucidated by observing reduced retinal vascular permeability in db/db mice after Nox4 was knocked down. According to the Genetics of Diabetes Audit and Research in Tayside Scotland datasets, which include 560 cases of type 2 diabetes and 4,106 controls, a strong association of the Nox4 gene with advanced diabetic retinopathy has been reported [73]. In line with these findings, Li et al presented findings indicating that Nox4 facilitates retinal neovascularization through the H2O2/VEGFR2/ERK signaling pathway in a mouse model of retinopathy. This evidence indicates that Nox4 is involved in advanced stages of retinopathy [74]. Few studies have explored Nox2 and Nox1 in diabetic retinopathy. Studies indicate that ROS from Nox1 potentially induce mitochondrial oxidative damage in retinal endothelial cells, triggering a metabolic memory cascade that contributes to diabetic retinopathy. Nox2, however, appears to be involved in early retinopathy stages [29].

Therefore, the activation of Nox subunits clearly plays a crucial role in the onset of diabetic retinopathy, with significant involvement in advanced stages. Among these subunits, Nox4 has been extensively studied, but reports on Nox1 and 2 are limited in this regard.

2.9. Nox in coronary artery disease (macrovascular complication)

Patients with diabetes have an increased risk of macrovascular diseases, including coronary artery disease, stroke, and peripheral vascular disease. The pivotal role of Nox enzymes in modulating vascular function in diabetes has been well established through prior studies conducted in both rodents and humans [75] Among the different Nox isoforms, it appears that ROS originating from Nox1 and Nox2 play significant roles in exacerbating the progression of atherosclerosis. Diabetic mice lacking the Nox1 and ApoE genes presented significantly reduced plaque areas in their aorta and aortic arch, suggesting a pro-atherosclerotic role of Nox1 [76]. Similarly, Judkins *et al.* [72] reported that the deletion of Nox2 in mice lacking the ApoE gene led to a decrease in ROS and an increase in NO availability, thereby reducing atherosclerotic plaque formation [78]. Consistent with these findings, Sukumar *et al.* [74] provided evidence of improved acetylcholine-induced vasodilation in Nox2-deleted mice [59]. In contrast to Nox1, Nox4 knockout in diabetic mice indicates that Nox4 does not play a proatherosclerotic role [76]. *In vivo* studies have demonstrated that diabetic mice lacking both the ApoE gene and Nox4 exhibit an increase in plaque area, suggesting that Nox4 plays a protective role against atherosclerotic plaque formation [77] However, *in vitro* studies have revealed a proliferative role of Nox5 in both endothelial cells and smooth muscle cells. Further observational studies have revealed associations between Nox5 and coronary artery disease, revealing elevated levels of Nox5 protein and gene expression [78].

In summary, the role of Nox subunits is multifaceted. Nox1 and Nox2 contribute to the progression of atherosclerosis, whereas Nox4 appears to play a protective role. However, further studies are needed to validate this concept and elucidate the precise mechanism involved, particularly concerning Nox4.

2.10. Preclinical evidence of Nox-mediated renal injury in DKD

To date, numerous experimental studies, including genetically modified models and cell culture models, have been conducted to elucidate the various types of damage caused to glomerular and tubular cells, as summarized in Table 2. The prevailing technique used to analyze cellular Nox expression involves Western blotting. The intracellular superoxide levels generated by Nox were quantified by using fluorescent dyes such as dihydroethidium and lucigenin, which undergo redox reactions upon interaction with superoxide, resulting in the emission of light. The intensity of the light emitted reflects the amount of superoxide produced within the cell. In addition, subsequent excretion of ROS markers, including 8-isoprostane (lipid peroxidation product) and 8-hydroxy-2′-deoxyguanosine (product of DNA oxidation), in urine has also been observed. The common method used for detection is ELISA. However, ELISA has several limitations, including limited sensitivity for ultralow-abundance biomarkers and potential cross-reactivity with structurally similar antigens, which can produce falsely low readings at high analyte concentrations. Recognizing these constraints is important to avoid overinterpreting preclinical oxidative stress data [33–34].

2.11. Nox inhibitors

Nox-mediated ROS play a significant role in DKD onset and progression (Fig. 2), prompting ongoing clinical trials to evaluate therapeutic agents aimed at modulating oxidative stress pathways, which are summarized in Table 3. Given the failed outcomes of traditional antioxidants in clinical trials for diabetic complications, current strategies emphasize mechanism-based redox therapies. These include selectively inhibiting specific ROS sources, enhancing endogenous antioxidant defenses, or repairing ROS-induced cellular damage and are now considered the state-of-the-art approach for future trials [79]

Table 2. Preclinical evidence of the role of Nox-mediated ROS in DKD pathogenesis.

Experimental Model	Nox isoform involved	Analysis of Nox expression	Analysis of Superoxide production	Significance
STZ-induced mice model [27]	Nox1	Western blot analysis	Electron spin resonance detection	Nox1, but not Nox2 or Nox4 mediates diabetic eNOS uncoupling for endothelial damage
STZ-induced rat model of DKD [31]	Nox4	lucigenin-enhanced chemiluminescence	Spectrophotometry was used to detect the ROS level by analyzing ferricytochrome c reduction that is inhibited by superoxide dismutase	Nox4 mediates the activation of Akt/PKB via Ang II and extracellular matrix protein synthesis in mesangial cells
STZ induced ApoE (-/-) mice [33]	Nox4	Immunofluorescence	Level of dihydroethidium in the renal cortex by HPLC L–012–derived chemiluminescence was used in Cytosol and mitochondrial level	Deletion of Nox4 showed renoprotection by reducing infiltration of proinflammatory and profibrotic factors
Human mesangial cell culture [34]	Nox1	Immunoblotting	Dihydroethidium and hydroxyphenyl fluorescence staining	The complete abolition of iNOS induction and subsequent mesangial fibrogenesis was observed only upon inhibition of NOX1
C57BL6/J mice [36]	Nox4	RT–PCR	Urinary 8-isoprostane by EIA	Nox4-mediated ROS generation activates PKC isoforms which in turn induce proteinuria
Transgenic Nox5pod+ mice [47]	Nox5	Western blot	Lucigenin assay	AngII-induced elevation of intracellular calcium levels, in turn, activates renal Nox 5 which mediates podocyte injury
human proximal tubular cell line HK-2 [53]	Nox1 Nox4	Western blot analysis for Nox1, Nox2 and Nox4 protein estimation	dichlorodihydrofluorescein diacetate assay for ROS estimation	High-glucose-induced EMT is mitigated by reducing intracellular ROS levels through the downregulation of Nox1 and Nox4, but not Nox2
Nox5 transgenic Akita mouse model of DKD [59]	Nox5	Western blot analysis for Nox5 protein level	Dihydroethidium staining for superoxide	Silencing of Nox5 resulted in a significant reduction in the expression of TLR-4 and MCP-1 and subsequent injury
Wild-type (C57Bl6/J), ApoE−/−, and Nox2−/y/ApoE−/− mice [74]	Nox2	Western blot analysis for Nox2	L012-enhanced chemiluminescence for ROS level	Nox2 contributes to elevated superoxide production, reduced NO bioavailability, and atherosclerotic plaque formation in DKD.
Floxed Nox4 [12]	Nox4	Western Blot analysis	Urinary 8-isoprostanes and 8-hydroxy-2′-deoxyguanosine by ELISA	Nox4 appears to be the major part of podocyte injury by activating PKC-isoforms

STZ: Streptozotocin; DKD: Diabetic kidney disease; Nox: NADPH oxidase; EMT: Epithelial mesenchymal transition; ROS: Reactive oxygen species; MCP-1: Monocyte chemoattractant protein-1; TLR4: Toll-like receptor-4; eNOS: Endothelial nitric oxide synthase; NO: Nitric oxide
ELISA: Enzyme-linked immunosorbent assay.

A new class of compounds called pyrazolopyridines has emerged, with remarkable specificity toward crucial targets such as ROS. Among these, GKT136901 and GKT137831 (Setanaxib) are designed with precision to interact selectively with NOX enzymes [80]

GKT136901 is a highly specific inhibitor of NADPH oxidase. It exhibits high potency against both Nox4 and Nox1 while maintaining 10-fold selectivity over Nox2. In particular, GKT-136901 significantly inhibited both Nox4 and Nox1 by 82% and 86%, respectively, with a partial inhibitory effect on Nox2 (60%) [81], which was confirmed by Sedeek *et al.* [80] who reported that pretreatment of mouse proximal tubular cells with GKT136901 inhibited the glucose-induced Nox4-induced activation of p38MAP kinase [82] A further inhibitory effect of the Nox1/4 inhibitor GKT136901 was evident in treated db/db mice via a reduction in albuminuria, the level of thiobarbituric acid-reacting substances in plasma and urine, which serve as a marker of oxidative stress, and a reduction in renal structural abnormalities compared with those in nontreated db/db mice [50,83].

GKT137831 has also been shown to have broad-spectrum renoprotective effects in a mouse model. It effectively reduces albuminuria, glomerular hypertrophy, mesangial matrix expansion, and podocyte loss at doses of 10 or 40 mg/kg [84]. However, Jha *et al.* [12,36,39,59,60] compared the effects of Nox1 or Nox4 gene deletion, along with pharmacological inhibition of Nox1/4 via GKT137831, and reported that the renoprotective effects of GKT137831 closely resembled Nox4 deletion rather than Nox1 deletion [84] In addition, GKT137831 treatment of human aortic endothelial cells cultured under hyperglycemic conditions reduced macrophage infiltration and the expression of proinflammatory cytokines, including MCP-1, and attenuated atherosclerosis development [85], suggesting that GKT137831 not only provides renoprotection but also prevents macrovascular complications. GKT137831 not only serves as a dual inhibitor that targets both the Nox1 and Nox4 isozymes but also partially inhibits Nox5 [36]. Supported by robust preclinical evidence, **GKT137831** has successfully completed phase I safety trials. More recently, a phase IIb study in patients with type 2 diabetic nephropathy was conducted, which, although it did not demonstrate a reduction in albuminuria, revealed significant decreases in biomarkers of inflammation and reactive oxygen species [12].

Recently, APX-115 (also known as Ewha-18278) was identified as a novel orally active pan-Nox inhibitor that acts

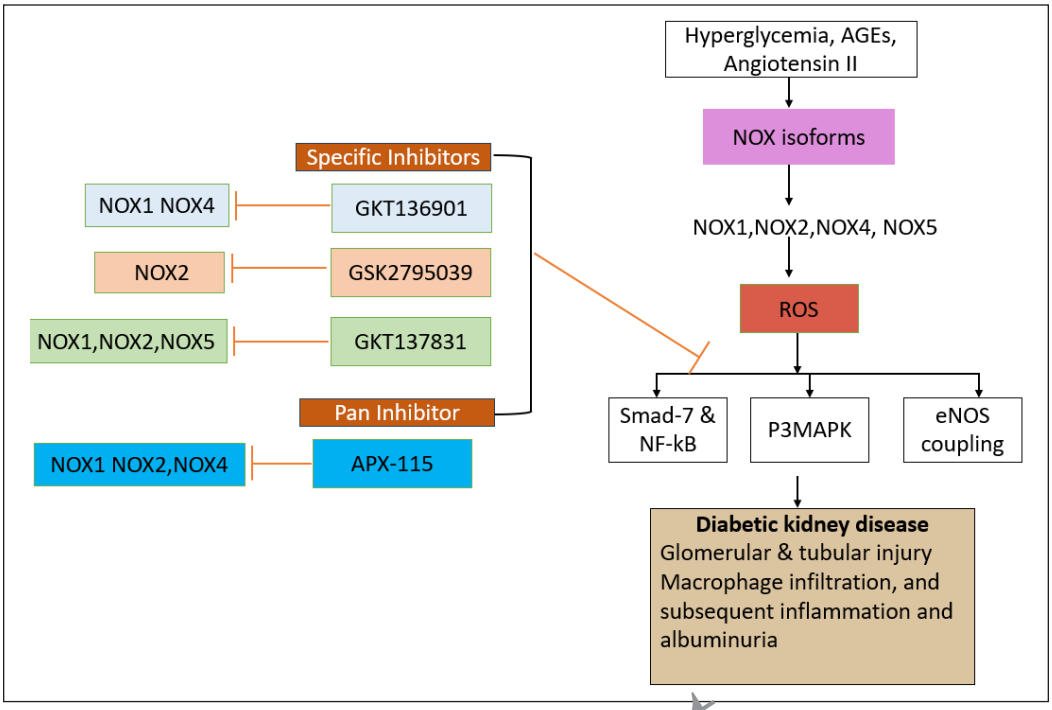

Figure 2. Overview of Nox mediated DKD progression.

Table 3. Nox Inhibitors in DKD.

Nox Inhibitors	Targets	Mode of action	Inhibitory effects
GKT136901 [86]	Nox1	Inhibit p38MAP kinase/direct scavenger of peroxynitrite	The treated arm showed a reduced level of oxidative markers in plasma and urine
	Nox4		
GSK279503 [12]	Nox2	Competitive inhibition of Nox2	Inflammatory signaling
GKT137831(Setanaxib) [83]	Nox1	Competitive inhibition	Podocyte injury, macrophage infiltration, and subsequent inflammation and albuminuria
	Nox4		
	Nox5		In addition, protective role against macrovascular complications of diabetes
GLX351322 [89]	Nox4	Not fully evaluated	Counteract glucose intolerance by reducing palmitate-stimulated insulin release
Apocynin [82]	Nox2	Inhibit renal expression of p47phox	Reduce lipid peroxidation products in plasma and albuminuria
Plumbagin [12]	Nox4	Inhibits Nox4-mediated inflammatory signaling pathways	Antiatherosclerosis and renoprotection by reducing the ECM proteins and albuminuria
Probucol [19]	Nox2	Free radical scavenger	Podocyte injury and albuminuria
APX-115 [86]	Nox1	Direct inhibition	Preserved the renal structure by reducing mesangial expansion, macrophage infiltration, and fibrosis,
	Nox2		
	Nox4		

ECM: Extracellular matrix; Nox: NADPH oxidase.

against multiple isoforms and has shown efficacy in protecting against renal injury in diabetic kidney cells. In diabetic mice, APX-115 treatment significantly improved insulin resistance, reduced oxidative stress, as indicated by decreased plasma 8-isoprostane levels, reduced urinary albumin excretion, and preserved renal structure. Moreover, comparative analysis demonstrated that APX-115 outperformed the dual GKT137831 in terms of efficacy [79]. In a comparative study of APX-115 and losartan in a diabetic mouse model, treatment with APX-115 showed efficacy comparable to that of losartan, and APX-115 effectively inhibited renal oxidative changes, including glomerular, tubular, and inflammatory alterations. These findings suggest that compared with inhibitors targeting specific Nox isoforms, pan-Nox inhibitors could offer superior therapeutic benefits for treating DKD. In various kidney cells, multiple Nox isoforms are present in an overlapping manner. In this context, the inhibition of protein expression of all Nox isoforms by APX-115 represents a promising therapeutic approach over Nox-specific inhibitors [86].

Setanaxib and APX-115 have advanced to human clinical trials. GKT137831 (NCT02010242), which is administered orally up to 200 mg twice daily for 12 weeks, is well tolerated in patients with diabetic nephropathy. All-cause mortality was 0%, and serious adverse events occurred in 4.4% of the treated participants versus 7.4% of the placebo-treated participants. The reported events were mild and included noncardiac chest pain, pneumonia, and hypoglycemia, indicating a favorable overall safety profile [87].

Nox inhibition alone is unlikely to be sufficient as a stand-alone therapy for DKD, given the multifactorial mechanisms underlying disease progression, including hyperglycemia, hemodynamic stress, advanced glycation end products, renin–angiotensin–aldosterone system (RAAS) activation, and inflammation. While Nox isoforms appear to be central drivers of oxidative stress in renal tissue, their inhibition would primarily target one arm of the pathogenic pathways. A more promising strategy is to integrate Nox inhibition with existing standard-of-care treatments, such as RAAS blockade, SGLT2 inhibitors, or anti-inflammatory agents, which together could address complementary pathways. Combination approaches may also mitigate the modest clinical effects observed thus far with Nox inhibitors alone, such as the reduction in oxidative stress and inflammatory markers without a significant impact on albuminuria [86].

Among the various cellular sources of ROS, Noxs are unique in that their primary function is to generate ROS, unlike most other enzymes, where ROS arise only as secondary byproducts or through dysfunction. This distinct role positions Nox enzymes as promising therapeutic targets in disorders driven by aberrant ROS signaling. Because of this potential, multiple Nox inhibitors have been developed, and the World Health Organization has recently introduced the term "-naxib" to designate this emerging drug class. Notably, this recognition coincided with the initiation of clinical trials evaluating setanaxib, the first-class Nox inhibitor [88].

However, whether Nox inhibition is safe and effective in long-term human studies remains uncertain, as current evidence is limited to short-duration trials. The chronic suppression of ROS pathways also raises potential safety concerns, including effects on liver function and physiological redox balance, which may only become evident with prolonged exposure [87]. These considerations highlight the need for large, long-term trials that integrate pharmacogenomic profiling and biomarker-based stratification to identify patient subgroups most likely to benefit from Nox inhibition while minimizing risk [89].

3. CONCLUSION

The cumulative function of different Nox isoforms and subsequent intrarenal oxidative stress critically contributes to the onset and progression of DKD through diverse cellular signaling cascades. Among the seven isoforms, Nox4 and Nox5 are pivotal for triggering glomerular injury, whereas Nox4 and Nox1 contribute to tubular injury. Both Nox4 and Nox5 play significant roles in orchestrating renal inflammation. In other complications of diabetes, Nox2 is linked to the initial stages, whereas Nox4 is involved in advanced stages. In addition, Nox4 appears to play a protective role in atherosclerosis, whereas Nox1 and Nox2 promote its progression. Despite substantial progress in exploring the involvement of Nox isoforms in DKD and its associated complications, more conclusive evidence from long-term follow-up studies is needed to confirm the conflicting findings from studies concerning Nox1 and Nox2. Because rodents lack Nox5, mechanistic insights into its role in DKD progression must rely primarily on studies using human cells and tissues. Numerous preclinical studies have shown the potential utility of urinary oxidative stress markers in diagnosing Nox-mediated renal injury in DKD patients, although this requires further validation. Among Nox inhibitors, pan-Nox inhibitors appear to be more effective than Nox-specific inhibitors in preventing the progression of DKD. The interconnected inflammatory network in DKD, driven by NOX enzymes and complementary pathways, implies that effective therapy will likely require multitarget strategies rather than single-agent approaches.

4. AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

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All the data is available with the authors and shall be provided upon request.

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The authors declare that they have not used artificial intelligence (AI)-tools for writing and editing of the manuscript, and no images were manipulated using AI.

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