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**Review Article**

# A brief study of Nox 4 inhibitors in diabetic nephropathy

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## ABSTRACT

The purpose of the study was to find the merits and demerits of NADPH oxidase 4 (Nox 4) inhibitors. Nox inhibitors are tested from natural sources like green tea, plumbagin, Chinese formulas like *Baoshenfang*, *Cudrania tricuspidata*, *Huangqi* decoction and synthetic dual Nox inhibitors. Some of them activate and regulate AMP-activated protein kinase (AMPK). Some chunk the high glucose activated alleyway, dawdling the succession of diabetic nephropathy (DN). Overall, the benefits of NOX are: reducing oxidative damage, improving renal function, reducing podocyte injury, preventing interstitial fibrosis, regulating AMPK which inhibits reactive oxygen species (ROS) and transforming growth factor-beta (TGF-beta), decreasing inflammation due to high glucose, protecting mesangial cells, decreasing collagen synthesis, and reducing glomerular hypertrophy. While targeting NOX in renal impairment, off-target effects, especially cardiovascular effects, are one of the major hurdles since diabetes mellitus (DM) is associated with co-morbid cardiovascular problems.

**Keywords:** Diabetic nephropathy, NADPH oxidase, NOX 4, Oxidative stress

## INTRODUCTION

### *Diabetes mellitus*

Diabetes is a chronic metabolic disease characterized by high levels of blood glucose (or blood sugar), which causes serious damage to the heart, blood vessels, eyes, kidneys, and nerves over time.[1-7] Type 2 diabetes is the most common, usually affects adults , and occurs when the body develops insulin resistance or fails to produce adequate insulin.[1-12] The occurrence of type 2 diabetes has increased spectacularly in countries of all income levels over the last three decades.[14] Type 1 diabetes, also cognized as juvenile diabetes or insulin-dependent diabetes, is a inveterate disease in which the pancreas fabricates very little or no insulin on its own.[15-17] Access to reasonably priced treatment, including insulin, is critical for people living with diabetes.[18-20] By 2025, there will be a global agreement to halt the rise in diabetes and obesity.[21]

Diabetes affects roughly 422 million individuals worldwide, with the preponderance living in low-and middle-income nations, and diabetes is directly accountable for 1.6 million deaths each year.[22] Diabetes has been gradually escalating in both the number of cases and occurrence over the last few decades.[22]

### *Diabetic nephropathy (DN)*

Diabetic nephropathy is a chronic condition that develops over time and is characterised by gradually increasing urinary albumin excretion (UAE), blood pressure and cardiovascular risk, falling glomerular filtration rate, and finally terminal renal disease (ESRD).[23]

### *Oxidative stress*

Oxidant species or reactive radicals are normally generated as by-products of normal cellular respiration/metabolism, and they play critical roles in

cellular processes such as signalling, ageing, and degenerative disease.[24] Anti-oxidant activity, which prevents potential harmful effects intermediate to excess oxidant accumulation, and oxidant species, which are considered to be essential signalling molecules for cellular physiology, coexist in perfect harmony in health.[24] Acute oxidative stress and subsequent tissue injury can be caused by factors that cause an inequality in the oxidant species/anti-oxidant equivalence, which can manifest itself in the form of augmented oxidant species production or significantly reduced anti-oxidant activity.[24] DN has been associated with a variety of pathophysiological mechanisms, with augmented oxidant species being acknowledged as the single amalgamating upstream incident.[25] In the pathophysiology of diabetic small blood vessel (microvascular) complications (retinopathy, nephropathy), oxidant species play a central and prominent role.[25]

***Oxidative stress in kidney***

In capillaries, functional modification of the interaction between glomerular capillary endothelial cells and their glycocalyx layer, as well as the interaction between podocytes, occurs.[25] All layers of the glomerular filtration apparatus are damaged by oxidant species.[25] Afterwards, extracellular matrix dumping is observed, which is primarily characterised by an augmented expression of type IV collagen.[25] Furthermore, the endothelial cell glycocalyx, which is primarily composed of proteoglycans and glycosaminoglycans with heparan sulphate and is recognised as a fundamental component of the glomerular filtration apparatus, is the most important target for reactive oxygen species.[25] Exceedingly high levels of hydrogen peroxide result in the detachment of heparan sulfate from glycosaminoglycans and/or dilapidation of glycosaminoglycans, a secondary decrease in anionic charges, and an augmented ability of the kidneys to permeate macromolecules.[26]

***NADPH oxidase***

The induction of matrix metalloproteinases and the inhibition of endogenous protease inhibitors are mediated by free radicals produced by oxygen and nitrogen, which has been predicted as a potential mechanism for glycocalyx dilapidation.[27] The GBM, which is known to safeguard surface charge for the anionic heparan sulphate side chains appended to the core proteins agrin and perlecan, and the fine ground substance (ECM) topology, which is crucial to preserving the selectivity of filtering molecules, can be targets of surplus oxidant species fabrication.[27] Hydroxyl radicals and other reactive species have been implicated in the breakdown of the polymeric chains of heparan sulphate and proteoglycan proteins, as well as protein dilapidation and cross-linking of type-IV collagen, both of which are directly involved in the preservation of the GBM's permeability discriminating properties.[27] High levels of glucose and fatty acids in free form (FFA) in the blood have been found to be powerful activators of NADPH oxidase enzymes in diabetes research models.[27] The RAAS has been noticed as one of the most imperative activators of NADPH oxidase and oxidant species ontogeny (origin and development).[27,28] The diabetic kidney has been meticulously acknowledged for its powerful and standard role in the fabrication of vascular and renal reactive species.[27,28] The physical link between NADPH-mediated superoxide anion and hydrogen peroxide synthesis and diabetic nephropathy pathogenesis is clear, as manifested by the augmented appearance of NADPH oxidase subunits in diabetic kidneys.[27,28] The Nox 4 subtype has been recognized as the key basis of renal reactive species causing diabetic nephropathy, and has been the subject of extensive methodical investigation in recent years.[28] In investigational replicates of diabetic nephropathy, inhibiting Nox 4 activity resulted in decreased oxidative stress and renal tissue injury.[28] Nox 4 antisense oligonucleotides treatment reduced renal hypertrophy and mesangial cell expansion in diabetic animal replicates.[28] In animal replicates of DN, the renoprotective effects of knocking down Nox 4 were linked to a reduction in glomerular damage.[28]

***Nox in DN***

Diabetic nephropathy is characterized by oxidative damage, inflammation, and apoptosis. Reactive oxygen species (ROS), superoxide anion, and hydrogen peroxide ($H_2O_2$) all play essential roles in various cellular alleyway networks.[29] Amplified productions of ROS is thought to be a major downstream alleyway of end organ injury. [29] Noxs, which include the isoforms Nox 1 to 5, as well as Duox 1 and 2, cause DN. [29]

NOX-derived ROS acts as a mediator of kidney injury in a variety of hypertension and diabetes models.[29] The kidney cortex expresses at least three different Nox isoforms, including Nox 4, Nox 2, and Nox 1. Nox 4 appears to be the most enriched with Nox. The Nox 4 isoform is over expressed in diabetic experimental models, and Nox 4 inhibition decreases glomerular expansion (hypertrophy), fibronectin fabrication, and proteinuria in diabetic models, implying a role for Nox 4-derived ROS in the pathogenesis of DN.[29]

***Nox inhibitors***

Studies on the role of the NADPH oxidases Nox 1 and Nox 4 in diabetic nephropathy: genetic deletion and pharmacological inhibition. Fluorofenidone (AKF-PD) is a new drug that has been shown to slow the progression of DN. In DN, Nox 4 deletion reduces oxidative stress and injury via PKC associated mechanisms. Crocin (paracetamol) improves kidney physiology by decreasing Nox 4, IL 18, and p53 expression levels in a DN experimental model. In an experimental model of DN, fenofibrate improves kidney physiology by improving NOX 4, IL 18, and p53 appearance. In an animal replicate of type 2 DN, probucol inhibited Nox 2 expression and

reduced podocyte injury. In diabetic nephropathy, the Baoshenfang formula reduces podocyte injury by inhibiting the Nox-4/ROS/p38 alleyway. In an animal model, APX-115, a first-in-class pan-Nox inhibitor, protects against kidney injury. Resveratrol inhibits diabetic nephropathy and kidney interstitial fibrosis by regulating the AMPK/Nox 4/ROS alleyway. Plumbagin alleviates diabetic nephropathy by interfering with Nox 4 signaling alleyways. By quashing Nox-mediated oxidative stress and kidney inflammation, protocatechuic aldehyde quashes cisplatin-induced acute kidney injury. Melatonin's renoprotective effect is demonstrated in an animal model (Zucker diabetic fatty rats) due to its thwarting action on Nox. Delphinidin hampers Nox-1 and mitochondrial free radicals (superoxide radicals) in kidney mesangial cells, thwarting high glucose (HG) provoked cell propagation and collagen production.[75]

Green tea (*Camellia sinensis*) reduces nephropathy in a diabetic animal model by down-regulating Nox 4 NADPH oxidase. Huidouba reduced podocyte injury in DN rats by down-regulating Nox 4 expression. Pitavastatin reduces albuminuria and kidney mesangial expansion in db/db mice by down-regulating Nox 4. Pharmacological inhibition of albuminuria and matrix accumulation with the dual Nox 4/Nox 1 inhibitor GKT137831 reduces albuminuria and matrix accumulation. In streptozotocin-induced diabetes rats, glycine reduces kidney oxidative stress by repressing Nox 4 expression. Naringin is used to manage diabetic nephropathy by inhibiting NADPH oxidase 4. The amplification in AMPK caused by cocoa has been revealed to be renoprotective in investigational diabetes mellitus by reducing Nox 4/TGF-1 alleyway. In a streptozotocin-induced diabetic rat model, valsartan reduces Nox 4 expression and prevents diabetic nephropathy. Zingerone reduces diabetic nephropathy by inhibiting the enzyme NADPH. Puerarin reduces diabetic kidney injury by controlling Nox 4 expression in podocytes.

*Cudrania tricuspidata* root extract reduces methylglyoxal-induced inflammation and oxidative stress via the PKC-Nox 4 Alleyway in vitro and in vivo.[86] Huangqi decoction inhibits hyperglycemia-induced podocyte apoptosis by down-regulating the Nox 4/p53/Bax alleyway. Farrerol protects kidney mesangial cells from HG-induced injury via the ROS/Nox 4/ERK1/2 pathway.[30-44]

*Advantages*

It slows the development of DN, reduces oxidative damage, improves renal function, reduces podocyte injury, prevents interstitial fibrosis, regulates AMPK, which inhibits ROS and TGF-beta, inhibits HG mediated activation of the ROS pathway, reduces albuminuria, decreases extracellular matrix deposition, decreases inflammation due to high glucose, protects mesangial cells, decreases collagen synthesis, reduces glomerular hypertrophy and, reduces fibronectin.[22-44]

*Disadvantages*

When tubular cells, cardiomyocytes, endothelial cells, and blood vessel (vascular) smooth muscle cells are injured, Nox 4 performs a cytoprotective and regulates metabolism.[89] With the advent of pharmacological Nox 4 inhibitors in clinical trials, caution should be exercised in identifying potential side effects in patients who are predisposed to acute kidney injury and cardiovascular injury.[45]

*Precaution*

In clinical trials of pharmacological Nox 4 inhibitors, caution should be implemented in identifying potential side effects in patients with known ischemic heart disease, post myocardial infarction, and atherosclerosis.[45]

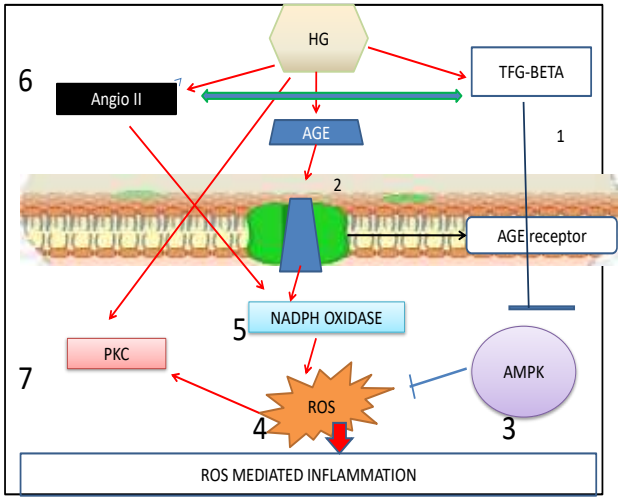


**Figure 1: Mechanism of Nox activation, inhibitions and action of various activators and inhibitors used in management of DN.[92-100]**

## DISCUSSION

Many potential targets are reviewed for diabetic nephropathy. Nox inhibitors are tested from natural sources like green tea, plumbagin, Chinese formulas like Baoshenfang, *Cudrania tricuspidata*, Huangqi decoction and synthetic dual Nox inhibitors. Some of them activate and regulate AMPK. Some block the high glucose activated pathway, slowing the progression of DN. Overall, the benefits of Nox are: reducing oxidative damage, improving renal function, reducing podocyte injury, preventing interstitial fibrosis, regulating AMPK which inhibits ROS and TGF-beta, decreasing inflammation due to high glucose, protecting mesangial cells, decreasing collagen synthesis, reducing glomerular hypertrophy, and reducing fibronectin production.[22-57]

*Future challenge*

While targeting Nox renal impairment, off-target effects, especially cardiovascular effects, are one of the major hurdles, since DM is associated with co-morbid cardiovascular problems.

## CONCLUSION

Nox inhibitors have the following benefits: quashing oxidative damage, mending renal function, reducing podocyte injury, thwarting interstitial fibrosis, regulating AMPK, which suppresses ROS and TGF-beta, decreasing inflammation caused by high glucose, shielding mesangial cells, inhibiting collagen synthesis, inhibiting glomerular hypertrophy, and inhibiting fibronectin production. Off-target effects, especially on the cardiovascular system, are a substantial obstacle to Nox therapy in renal impairment, given that diabetes is associated with co-morbid cardiovascular issues.

***Recommendations***

Nox inhibitors can be game changers in the management of DN provided cardiovascular and other off-target effects are overpowered.

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