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REVIEW ARTICLE

Reno-protective effects of Phosphodiesterase 5 inhibitors

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Abstract
The kidneys are vital organs that play an important role in removing waste materials from the blood, electrolyte balance, blood pressure regulation, and red blood cell genesis. Kidney disease can be caused by various factors, including diabetes, ischemia/reperfusion injury, and nephrotoxic agents. Inflammation and oxidative stress play a key role in the progression and pathogenesis of kidney diseases. Acute kidney injury (AKI) and chronic kidney disease (CKD) are important health problems worldwide, as they are associated with a long-term hospital stay, and increased morbidity and mortality in high-risk patients. Current standard therapeutic options are not sufficient to delay or stop the loss of kidney function. Therefore, it is necessary to develop new therapeutic options. Phosphodiesterase 5 inhibitors (PDE5Is) are a currently available class of drugs that are used to treat erectile dysfunction and pulmonary hypertension in humans. However, recent evidence suggests that PDE5Is have beneficial renoprotective effects via a variety of mechanisms. In this review, the benefits of PDE5 inhibitors in clinical conditions associated with kidney disease, such as diabetic nephropathy, ischemia–reperfusion injury, and acute and chronic kidney injury, are summarized.

Keywords Phosphodiesterase inhibitors · Kidney protection · Ischemia–reperfusion injury · Diabetic nephropathy · Chronic kidney disease

Introduction

The kidney is a vital organ that has many functions, including electrolyte and volume regulation, elimination of nitrogenous wastes, elimination of exogenous molecules (e.g., many drugs), synthesis of various hormones (e.g., erythropoietin), and metabolism of low molecular weight proteins. Renal failure develops in cases where the kidneys fail to fulfill their excretory function or when there is an increase in nitrogenous waste products in the blood. There are two types of kidney failure, which are acute and chronic kidney failure [1].

Acute renal failure (ARF) is a syndrome in which glomerular filtration is often reversibly decreased (hours to days). According to "Kidney Disease: Improving Global Outcomes (KDIGO)," which was written in 2012, acute kidney injury (AKI) is diagnosed when an individual has either (a) increased creatinine 0.3 mg/dL in 48 h, (b) creatinine 1.5 times baseline in the last 7 days or (c) urine volume less than 0.5 mL/kg per hour for 6 h [2]. 'AKI' often replaces the term 'ARF,' as it expresses the entire clinical spectrum (e.g., from a slight increase in serum creatinine to overt renal failure, [3]. The causes of AKI can be prerenal, intrarenal, and postrenal. Prerenal AKI accounts for about 60% of AKI cases, and its causes include hypotension, volume constriction (e.g., bleeding, sepsis), severe organ failure (e.g., heart and liver), and drugs (e.g., nonsteroidal anti-inflammatory drugs (NSAIDs), angiotensin receptor blockers (ARB), angiotensin-converting enzyme inhibitors (ACEIs), and cyclosporine). Intrarenal AKI accounts for approximately 35% of AKI cases and is caused by acute tubular necrosis (e.g., nephrotoxic substances, radiographic contrast agent, prolonged prerenal insufficiency), acute interstitial nephritis, connective tissue disorders (e.g., vasculitis), fat embolism, intrarenal deposition (e.g., tumor lysis syndrome, increased uric acid production, and multiple myeloma), and rhabdomyolysis.

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Postrenal AKI is responsible for approximately 5% of AKI cases and can be caused by extrinsic compression (e.g., prostatic hypertrophy, carcinoma), intrinsic obstruction (e.g., stone, tumor, clot, stricture), and neurogenic bladder [1].

Chronic kidney disease (CKD) is a permanent clinical syndrome with a slow and progressive nature that is characterized by the irreversibility of the kidney's function and/or structure. CKD is one of the most common metabolic diseases in all societies. According to the US Annual Data Report of the 2015 Renal Data System, the prevalence of CKD ranges from 3.5 to 14% [2]. CKD is diagnosed in adult patients with a glomerular filtration rate (GFR) of less than 60 ml/min/1.73 m^2 for at least three months or in those with a GFR greater than 60 ml/min/1.73 m^2 with evidence of kidney damage. Signs of kidney damage include albuminuria (i.e., more than 30 mg of albumin in 24 h urine), hematuria/leukocyturia, histological changes in kidney biopsy, changes in kidney imaging, persistent hydroelectrolytic disturbances, and previous kidney transplants [4]. The main causes of CKD include hypertension, diabetes, autoimmune diseases, chronic pyelonephritis, chronic glomerulonephritis, polycystic kidney disease, chronic use of anti-inflammatory drugs, congenital malformations, and long-term acute kidney disease [4].

CKD, end-stage renal disease (ESRD), and kidney transplantation affect the endocrine system, thereby causing a wide variety of syndromes and clinical disorders. CKD has an effect on fertility by causing uremia, chronic inflammation, and changes in reproductive hormone levels in both men and women. Sexual dysfunction, such as erectile dysfunction, decreased libido, and decreased frequency of sexual intercourse are common in patients with CKD [5]. One of the most common symptoms of sexual dysfunction in men with CKD is erectile dysfunction (ED). The prevalence of ED has been reported to be 70–80% in dialysis patients [6]. A multinational cross-sectional study of 946 men undergoing hemodialysis reported that 83% of those men had varying degrees of erectile dysfunction [7].

In the aging population, the high incidence of diabetes and hypertension has led to an increase in the number of patients with CKD [8]. However, currently available standard treatment options are not sufficient to prevent the progression of CKD in many patients. Therefore, new drugs are needed to slow the loss of kidney function. In recent studies, many agents have been utilized for the treatment of ESRD, CKD or diabetic nephropathy (DN). These include phosphodiesterase inhibitors (PDEI), anti-inflammatory agents, vitamin D receptor activators, nuclear factor erythroid 2–related factor 2 (Nrf2) activators, and endothelin receptor A blockers [9]. Among these therapeutics, PDEI (used for the treatment of ED) have shown promise in slowing down chronic renal failure. In this review, the renoprotective role of PDE 5 inhibitors was summarized.

Phosphodiesterase 5 inhibitors

PDE are a family of enzymes that regulate cellular levels of second messengers, such as cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) [10]. To date, eleven different PDE families have been defined [11]. Each PDE family has its own characteristics, and each modulates different regulatory pathways in the cell. Therefore, targeting specific PDE families may be helpful in treating diseases [11, 12]. PDEs 5, 6, and 9 are selective for cyclic 3-5-guanosine monophosphate (cGMP), PDEs 4, 7, and 8 are selective for cyclic 3-5-adenosine monophosphate (cAMP), and PDEs 1, 2, 3, 10, and 11 can hydrolyze both cAMP and cGMP [13].

PDE5 is found in high concentrations in the smooth muscle cells of the peripheral arteries and venous vessels, coronary and pulmonary circulation, vascular smooth muscle cells of the corpora cavernosa of the penis, as well as in platelets [10]. PDE5 specifically hydrolyzes cGMP (Fig. 1) [11]. The resulting cGMP activates cGMP-dependent protein kinase (cGK or Protein Kinase G (PKG),), which in turn activates certain proteins that cause various cellular effects, such as growth, vitality, endothelial permeability, ion transport, smooth muscle relaxation, secretion, and gene transcription. There are three isoforms of PDE5. PDE5A1

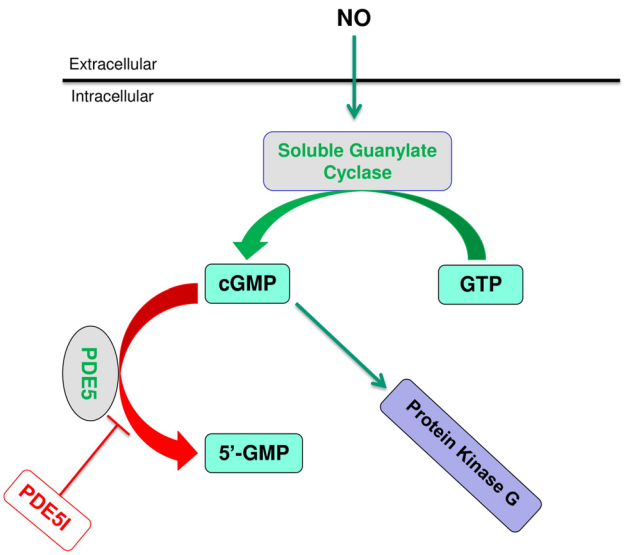

Fig. 1 cGMP signaling cascade. cGMP is produced by soluble guanylyl cyclases through nitric oxide activation. cGMP then activates cGMP-dependent protein kinase G, causing various cellular effects, such as growth, vitality, endothelial permeability, ion transport, smooth muscle relaxation, secretion, and gene transcription. PDE5 specifically catabolize cGMP. PDE5I, on the other hand, increases the cGMP activity by inhibiting this effect of PDE5

and PDE5A2 are widely expressed in the brain, lung, vascular smooth muscle cells, and tubular epithelial cells of the renal proximal tubule and medullary collecting duct, whereas PDE5A3 is only expressed in vascular smooth muscle cells [14].

PDE5 inhibitors (PDE5Is) increase intracellular cGMP by selectively inhibiting PDE5-driven cGMP hydrolysis. cGMP is the second messenger for both the natriuretic peptide system as well as nitric oxide (NO). Increased cGMP causes prolongation of the NO signal in vascular smooth muscle cells, causing smooth muscle relaxation and vasodilation [15]. As a result, vasodilation in the corpus cavernosum of the penis supports erection, while vasodilation in the pulmonary vessels decreases their pressure and decreases arterial blood pressure in the systemic circulation [16]. Zaprinast, which was synthesized in 1974, was identified as the first selective PDE5 inhibitor [17]. However, later studies revealed that zaprinast is actually not selective for PDE5 [18]. The Food and Drug Administration (FDA) and the European Medicines Agency (EMA) introduced Sildenafil in 1998, vardenafil and tadalafil in 2003, and avanafil in 2013 as PDE5I compounds [19]. The pharmacological profile of PDE5I, which is used orally at therapeutic dosage in the treatment of ED, is shown in Table 1 [20].

Physiological role of PDE5 in the kidney

PDE5 is also expressed in renal vessels, glomeruli, internal medullary collecting ducts, and cortical tubules [21]. It is known that PDE5 inhibition regulates the excretory function and hemodynamics of the kidney. In the renal vascular wall, PDE5 contributes to the regulation of renal vascular blood flow by limiting the vascular relaxation caused by cGMP [22]. PDE5 contributes to the regulation of natriuresis through the degradation of cGMP. Chen et al. [16] showed that PDE5 inhibition raised cGMP and, more importantly, natriuresis in heart failure dogs. Similarly, in a study in pregnant rats, it was revealed that PDE5 activity reduced the natriuretic effect caused by the cGMP signal in the collecting duct [23]. Thus demonstrating that the PDE is a negative regulator for cGMP-mediated natriuresis.

Table 1 Pharmacological profile of oral PDE5I at therapeutic dosage for ED [20]

Parameter	Sildenafil 100 mg	Tadalafil 20 mg	Vardenafil 20 mg
T_{max} (h)	1.16 ± 0.99	2	0.66 (0.250–3.0)
$T_{1/2}$ (h)	3.82 ± 0.84	17.5	3.94 ± 1.31
C (max ng/m)	327 ± 236	378	20.9 ± 1.83
AUC (ng × h/m)	1963 ± 859	8066	74.5 ± 1.82

PDE5I Phosphodiesterase type-5 inhibitor, *ED* Erectile dysfunction

NO-cGMP-PDE5 controls glomerular filtration by regulating cleft membrane and cytoskeletal reorganization in podocytes [24]. In juxtaglomerular (JG) cells, while renin synthesis is stimulated by cAMP, it is inhibited by cGMP [25]. PDE5 increases renin synthesis by degrading cGMP in JG cells [26]. Since PDE5 is widely found in kidney tissue and is involved in kidney physiology and clinical and experimental studies have shown that it may play a role in kidney damage, it shows that PDE5I can play a potential role in the management of kidney disease. However, there is currently no PDE5I approved and marketed for the treatment of kidney disease [13].

Renoprotective effect of PDE5 inhibitors in diabetic nephropathy

The incidence of diabetes mellitus and its most important complication, diabetic nephropathy (DN), is increasing worldwide [24]. DN is characterized by oxidative stress, podocyte damage, and glomerulosclerosis [27]. In addition, there is reduced NO bioavailability in DN, which may play an important role in disease progression. However, the detailed pathophysiological mechanism has not been fully elucidated. The NO-cGMP axis has been reported to be important in maintaining glomerular filtration and renal perfusion [28]. In vascular endothelial cells, NO is synthesized from L-arginine by endothelial NO synthase (eNOS). The majority of NO's biological actions are mediated by cGMP. The cGMP hydrolyzing enzyme, PDE5, is expressed in the proximal tubules, collecting ducts, and glomerulus in the kidney [29]. The NO-cGMP axis contributes to glomerular filtration by regulating the cleft membrane and cytoskeletal reorganization in podocytes [30]. In diabetic patients, it has been shown that cGMP production is decreased in the glomeruli [31]. The causes of NO-cGMP dysfunction in DN include the removal of NO by reactive oxygen species (ROS) [32] and increased activity of PDE5, which is reported to be the main cGMP hydrolyzing enzyme in rat glomeruli [33]. However, increased cGMP levels due to selective PDE5 inhibition has been shown to reduce glomerulosclerosis and proteinuria in various kidney disease models, including animal models of both type 1 and type 2 diabetes [15, 34].

Results of some studies investigating the effects of PDE5 inhibitors on DN are shown in Table 2. Most of these studies were conducted on the PDE5I sildenafil. Sildenafil has been shown to improve albuminuria, glomerular hyperfiltration, glomerular hypertrophy, glomerulosclerosis score, levels of serum urea and creatinine (Cr), NO, malondialdehyde (MDA), glutathione (GSH), glutathione peroxidase (Gpx), superoxide dismutase (SOD), catalase (CAT), total antioxidant status (TAS), monocyte chemotactic protein-1 (MCP-1), and inflammation and monocyte/macrophage infiltration (ED-1) levels in DN [15].

Table 2 Renoprotective effect of PDE5I in diabetic nephropathy

Author, year	Study design	PDE5I	Diabetic nephropathy	Renoprotective effects of PDE5I
Lau et al. 2007	Animal (Rabbits)	Vardenafil (3 mg/kg/day)	↑sCr, ↑Proteinuria, ↓CrCl	↓sCr, ↓Proteinuria, ↑CrCl
Jeong et al. 2009	Animal (Sprague–Dawley rats)	Sildenafil (3 mg/kg/day)	↑Nitrotyrosine, ↑MCP-1, ↑ED-1, ↑iNOS ↑Albuminuria, ↑Urine 8-OH dG	↓Nitrotyrosine, ↓MCP-1 ↓ED-1, ↓iNOS Albuminuria, ↓Urine 8-OH dG, ↓
Kuno et al. 2011	Animal (Sprague–Dawley rats)	Sildenafil (2.5 mg/kg/day)	↑Albuminuria, Glomerulosclerosis + Glomerular Hyperfiltration + Glomerular Hypertrophy + ↑Collagen Types I, ↑Collagen Types III	↓Albuminuria, GlomerulosclerosisØ Glomerular HyperfiltrationØ Glomerular HypertrophyØ ↓Collagen Types I, ↓Collagen Types III
Qi et al. 2011	Animal (Sprague–Dawley rats)	Icariin (80 mg/kg)	↑Collagen IV, ↑TGF-β1, ↑sCr, ↑BUN, ↑MDA, ↓SOD,↑Hydroxyproline, Glomerular Hypertrophy +	↓Collagen IV, ↓TGF-β1, ↓sCr, ↓BUN, ↓MDA, ↑SOD, ↓Hydroxyproline, Glomerular HypertrophyØ
Tripathi et al. 2015	Animal (Sprague–Dawley rats)	Sildenafil (2.5 mg/kg/day)	↑Total protein excretion, ↑Albuminuria ↑sCr, ↑BUN, ↓CrCl, Glomerular sclerosis +	↓Total protein excretion, ↓Albuminuria ↓sCr, ↓BUN, ↑CrCl, Glomerular sclerosis Ø
Lee et al. 2015	Animal (Mouse Cell Culture)	Tadalafil (10 μM)	↑Glucose-induced Protein Synthesis, ↑mTORC1, ↑Laminin γ1, ↑Fibronectin ↓AMPK Phosphorylation	↓Glucose-induced Protein Synthesis, ↓mTORC1, ↓Laminin γ1, ↓Fibronectin ↑AMPK Phosphorylation
El-Mahdy et al. 2016	Animal (White Albino rats)	Sildenafil (3 mg/kg/day)	↑sCr ↑BUN, ↑Proteinuria ↑Kidney IL-1 β ↓NO, ↓SOD, ↓TGF-β1	↓sCr ↓BUN, ↓Proteinuria, ↓Kidney IL-1 β ↑NO, ↑SOD, ↑TGF- β1
Mehanna et al. 2018	Animal (Sprague–Dawley rats)	Sildenafil (3 mg/kg/day)	↑MDA, ↑sCr, ↑BUN ↓GSH, ↓CAT, ↓GPx, ↓SOD, ↓TAS	↓MDA, ↓sCr, ↓BUN ↑GSH, ↑CAT,↑GPx, ↑SOD, ↑TAS
Wang et al. 2020	Animal (Sprague–Dawley rats)	Icariin (20, 40, 80 mg/kg)	↑Proteinuria, ↑BUN, ↑sCr, ↑Blood Pressure, ↑MDA ↑triglyceride, ↑LDL-C, ↓HDL-C, ↓CAT, ↓ SOD,	↓Proteinuria, ↓BUN, ↓sCr, ↓Blood Pressure, ↓MDA ↓triglyceride, ↓LDL-C, ↓HDL-C, ↑CAT, ↑SOD,

sCr serum creatinine, *BUN* Blood Urea Nitrogen, *SOD* superoxide dismutase, *TGF-β* transforming growth factor beta, *TNF-α* tumor necrosis factor α, *CrCl* Creatinine Clearance, *MCP-1* Monocyte chemoattractant protein-1, *ED-1* inflammation and monocyte/macrophage infiltration, *MDA* malondialdehyde, *NO* nitric oxide, *GSH* Glutathione, *CAT* catalase, *GPx* glutathione peroxidase, *TAS* total antioxidant status, *TOS* total oxidant status, *Urine 8-OH dG* urine. 8-hydroxy-2-deoxyguanosine, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *IL-1 β* Interleukin 1 beta, *AMPK* adenosine monophosphate-activated protein kinase, *mTORC1* mammalian target of rapamycin 1

Tadalafil, another PDE5I, protects podocytes from damage by inhibiting matrix protein synthesis caused by high glucose levels via the NO-Hydrogen sulfide- AMP-activated protein kinase- Mammalian target of rapamycin complex 1 (NO-H2S-AMPK-mTORC1) pathway [35]. Treatment with Vardenafil, another PDE5I, has been shown to improve serum creatinine concentration, proteinuria, podocyte cGMP levels, renal Transforming growth factor beta 1 (TGF-β1) expression, and renal NOS levels in DN [24, 34]. Further, administration of Icariin, another PDE5I, reduces intracellular superoxide anion levels, inhibits fibronectin formation, improves SOD, MDA, Blood Urea Nitrogen (BUN), Cr, 24 h proteinuria, microalbuminuria levels, and expression of TGF-β1 and collagen IV protein in DN [36, 37]. Taken together, these data indicate that PDE5I inhibitors have a renoprotective effect in DN.

Renoprotective effect of PDE5 inhibitors in ischemia–reperfusion injury

Ischemia is an irreversible process of tissue injury that is caused by loss of blood flow in the tissue due to a bloodstream disturbance [38]. The period when there is blood flow to the tissue after the ischemic period is termed 'reperfusion,' and it can cause severe tissue damage, which is known as 'ischemia reperfusion' (I/R) [39]. I/R-induced kidney damage is a common cause of acute kidney failure, which occurs in several conditions such as shock, heart failure, kidney transplantation, nephron-sparing surgery, and renal

angioplasty [40]. Although previous studies have elucidated the mechanisms underlying renal I/R injury, there are no effective treatments. Mechanisms of renal I/R injury include hypoxia, accumulation of free radicals (such as ROS), inflammatory cell infiltration, vascular endothelial damage, and the generation of inflammatory mediators. Studies have shown that I/R exacerbates renal structural damage [41]. PDE5 inhibitors have been reported to increase antioxidant defense, at the same time reducing inflammation and apoptosis [42].

Results of studies investigating the effects of PDE5 inhibitors on renal I/R damage are presented in Table 3. Among the PDE5I, most studies in renal I/R injury have been performed with tadalafil. Tadalafil especially improved tubular morphology, Intercellular Adhesion Molecule 1 (ICAM-1), MCP-1, serum BUN, Cr, C-reactive protein, MDA, SOD, Myeloperoxidase (MPO), levels of total oxidant status (TOS) and TAS, expression of caspase-3, Tumor necrosis factor alpha (TNF-α), Interleukin 1 beta (IL-1b), IL-6, apoptotic protease activating factor 1 (APAF-1), inducible NOS (iNOS), and eNOS and Heat shock protein 70 (HSP-70) levels in I/R renal injury [43–45].

The PDE5I Sildenafil has been shown to provide a renoprotective effect against I/R damage through its anti-inflammatory, antioxidant, and anti-apoptotic effects. Sildenafil treatment has been reported to ameliorate apoptotic cells, as well as improve eNOS levels, p53 positive cells, MDA, MPO, Thiobarbituric acid reactive substance (TBARS), superoxide anion production (SAG), GSH levels, caspase-3 expression, creatinine clearance (CrCl), BUN, TNF-α, IL-1β and ICAM-1 levels, and has also been reported to improve the histopathological damage score in I/R injury [46–49]. The administration of the PDE5I Vardenafil improves serum creatinine, fractional sodium excretion (FENa), renal tissue cGMP levels, renal scintigraphy, and histological score in I/R injury [50]. The PDE5I Udenafil has a protective effect against damage to histopathological findings and biochemical parameters (e.g., Cr, BUN, Crcl and neutrophil gelatinase-associated lipocalin (NGAL) levels) in I/R [51]. Taken together, these data indicate that PDE5 inhibitors have a renoprotective effect in I/R injury.

Renoprotective effect of PDE5 inhibitors in nephrotoxic nephropathy

Contrast-induced nephropathy (CIN) is an acute nephropathy syndrome that occurs within 48 h after exposure to intravascular iodinated contrast media (CM), which is typically given for diagnostic purposes [52]. CIN is associated with an increased risk of cardiovascular adverse events, prolonged hospital stays, and high mortality [53]. The pathophysiology of CIN is due to both direct cellular toxicity and locally decreased renal blood flow. Therefore, based on the putative pathophysiology of CIN, increasing renal blood flow via the induction of local vasodilation should be a viable treatment option. PDE5 inhibitors are thought to be effective in the treatment of CIN, as they have previously been shown to reduce ischemia-induced kidney damage [46]**.** In addition to treating CIN, PDE5Is have also been studied as treatments for renal damage caused by nephrotic agents (such as gentamicin, cisplatin, doxorubucin).

Results of studies investigating the effects of PDE5 inhibitors on nephrotoxic nephropathy are presented in Table 4. Treatment with the PDE5I sildenafil was associated with decreased histological damage, attenuation of acute kidney injury markers, decreased electrolyte disturbance, decreased plasma creatinine, uremia, and proteinuria, and decreased production of ROS, TAC, GSH, TBARS in CIN [54, 55]. The administration of Sildenafil has been reported to improve iNOS expression, serum Cr and urea levels, urinary albumin, and renal MDA, CAT and SOD activities in gentamicin-induced renal injury [56]. In doxorubicin-induced renal injury, sildenafil treatment causes a significant decrease in serum urea, Cr, and uric acid levels, a significant improvement in renal MDA and GSH levels, and a decrease in the amount of renal TNF-α [57]. Further, sildenafil administration causes a dramatic improvement in renal histopathology, increase in renal blood flow, increase in renal Bcl-2-associated X protein/B-cell lymphoma 2 (Bax/Bcl-2) ratio, decrease in renal caspase-3 activation and Terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) positive apoptotic cells when used as a treatment for damage caused by cisplatin, another nephrotoxic agent [58].

The PDE5I Tadalafil abolishes the increase in urinary NGAL excretion in patients given CM, suggesting a nephroprotective effect against contrast agent-induced AKI [59]. In addition, Tadalafil exerts a protective effect against renal damage in sepsis, as evidenced by both biochemical and histopathological analyses in serum and kidney tissue. This protective effect may be due to the fact that Tadalafil suppresses oxidative stress and inflammation, both of which can cause tissue damage [60]. Likewise, pretreatment with tadalafil has been shown to have a renoprotective effect in the Escherichia coli-induced pyelonephritis (PN) rat model. In that study, tadalafil completely cured PN-specific tubular damage and cast formation, greatly reversed oxidant/antioxidant system dysfunction, significantly altered the increase in plasma inflammatory cytokine and chemokine excretion, and attenuated the expression of the renal fibrotic biomarker TGF-β [61].

In cyclosporine A (CyA) -induced nephropathy, administration of the PDE5I Vardenafil improved expression levels of previously decreased Platelet-derived growth factor (PDGF)-A and C, TGF-β1, and cyclo-oxygenase 1 (COX-1) and -2 by modulating cGMP activity in the kidneys [62].

Table 3 Renoprotective effect of PDE5I in ischemia–reperfusion (I/R) injury

Author, year	Study design	PDE5I	I/R injury	Renoprotective effects of PDE5I
Guzeloglu et al. 2010	Animal (Wistar Albino rats)	Tadalafil (10 mg/kg)	↔ TAS, ↑TOS, Tubular necrosis, Intracytoplasmic vacuolization, congestion and mononuclear cell infiltration in medulla	↑TAS, ↔ TOS, Improved histological changes
Gasanov et al. 2011	Animal (Sprague–Dawley rats)	Tadalafil (1 mg/kg)	Glomerular Sclerosis, Tubular necrosis Interstitial edema, Hyaline degeneration Leucocyte infiltration in medulla	Improved histological changes
Kucuk et al. 2012	Animal (Sprague–Dawley rats)	Tadalafil (1 mg/kg)	↑iNOS, ↑eNOS, ↑apoptotic cells, ↑p53 positive cells, ↑MPO, ↑MDA Leucocyte migration, Tubular dilatation	↓iNOS, ↓eNOS, ↓apoptotic cells, ↓p53 positive cells, ↔ MPO, ↔ MDA Improved histological changes
Kyriazis et al. 2013	Animal (Wistar Albino rats)	Vardenafil (0.02, 0.2, 2, 20 μg/kg)	↑sCr, ↑FeNa, ↑Total histology score	↓sCr (0.2, 2,20 μg/kg), ↓FeNa(0.2, 2, 20 μg/kg), Improved histological changes
Erol et al. 2015	Animal (Wistar Albino rats)	Tadalafil (10 mg/kg)	↑MDA, ↓TAS, ↑APAF-1, ↑iNOS, ↑eNOS Loss of nucleus, Hyaline cast formation, Cell swelling, Brush border loss Tubular dilatation, Interstitial congestion	↓MDA, ↑TAS, ↓APAF-1, ↓iNOS, ↓eNOS Improved histological changes
Zahran et al. 2015	Animal (Sprague–Dawley rats)	Sildenafil (1 mg/kg)	↓Nrf 2 protein expression, ↓Nrf2/HO-1/NQO-1 ↓Bcl-2,↑sCr, ↑BUN, ↑TNF-α, ↑IL-1β,↑ICAM-1, Tubular necrosis, neutrophil infiltration	↑Nrf 2 protein expression, ↑Nrf2/HO-1/NQO-1 ↑Bcl-2, ↔ sCr, ↔ BUN, ↓TNF-α, ↓IL-1β, ↓ICAM-1, Improved histological changes
Sousa et al. 2015	Animal (Wistar Albino rats)	Vardenafil (1 mg/ml)	↑Cleaved caspase-3 ↑ vacuolar degeneration of tubular cells	↓Cleaved caspase-3 ↓ vacuolar degeneration of tubular cells
El-Sisi et al. 2016	Animal (Albino rats)	Tadalafil (5 mg/kg)	↑ICAM-1, ↑TNF-α, ↑IL-1β, ↑Caspase-3 ↑sCr, ↑BUN, ↑MDA, ↓SOD, ↑MPO Tubular necrosis	↓ICAM-1, ↓TNF-α, ↓IL-1β, ↓Caspase-3 ↓sCr, ↓BUN, ↓MDA, ↑SOD, ↓MPO
Mohey et al. 2016	Animal (Wistar Albino rats)	Sildenafil (0.5-1 mg/kg)	↓CrCl, ↓GSH, ↑BUN,↑Uric acid, ↑SAG, ↑TBARS, ↑FeNa ↑Plasma potassium levels, Glomerular damage, tubular dilation, atrophy, neutrophil accumulation	↑CrCl, ↑GSH, ↓BUN, ↓Uric acid, ↓SAG, ↓TBARS, ↓FeNa ↓Plasma potassium levels, Improved histological changes
Mederios et al. 2017	Animal (Wistar Albino rats)	Tadalafil (10 mg/kg)	↓ ICG signal, ↑TNF-α, ↑IL-1β, ↑IL-6 ↑plasma urea, ↑creatinine, ↑C-reactive protein	↑ICG signal, ↓ TNF-α, ↓ IL-1β, ↓ IL-6 ↓ plasma urea, ↓ creatinine, ↓ C-reactive protein
Ozmerdiven et al. 2017	Animal (Sprague–Dawley rats)	Tadalafil (1 mg/kg)	↑Glomerular HSP-70, ↑Tubular HSP-70, Renal tubular damage, Peritubular fibrosis	↔ Glomerular HSP-70, ↓Tubular HSP-70, Improved histological changes
Wietzikoski et al. 2017	Animal (Wistar Albino rats)	Tadalafil (10 mg/kg)	Leucocyte accumulation in cortical Interstitium	Improved histological changes
Ozlulerden et al. 2017	Animal (Wistar Albino rats)	Udenafil (10 mg/kg)	↑NGAL, ↑MDA, ↑BUN, ↑sCr ↑Histological damage score	↓NGAL, ↓MDA, ↓BUN, ↓sCr ↓Histological damage score
Zahran et al. 2019	Animal (Mongrel dogs)	Sildenafil (1 mg/kg)	↑caspase 3, ↑TNF-α, ↑IL-1β, ↑Nrf2, ↑ICAM-1 ↑sCr, ↑BUN, ↓eNOS, ↓GFR, interstitial fibrosis	↓caspase 3, ↓TNF-α, ↓IL-1β, ↓Nrf2, ↓ICAM-1 ↓sCr, ↓BUN, ↑eNOS, ↑GFR, Improved histological changes
Nam et al., 2020	Animal (Sprague–Dawley rats)	Tadalafil (5 mg/kg/day)	↑sCr, ↓eNOS, ↑ICAM-1, ↑MCP-1	↓sCr, ↑eNOS, ↓ICAM-1, ↓MCP-1

sCr serum creatinine, *BUN* Blood Urea Nitrogen, *SOD* superoxide dismutase, *TGF-β* transforming growth factor beta, *TNF-α* tumor necrosis factor α, *CrCl* Creatinine Clearance, *MCP-1* Monocyte chemoattractant protein-1, *ED-1* inflammation and monocyte/macrophage infiltration, *MDA* malondialdehyde, *NO* nitric oxide, *GSH* Glutathione, *CAT* catalase, *GPx* glutathione peroxidase, *TAS* total antioxidant status, *TOS* total oxidant status, *Urine 8-OH dG* urine. 8-hydroxy-2-deoxyguanosine, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *IL-1 β* Interleukin 1 beta, *AMPK* adenosine monophosphate-activated protein kinase, *mTORC1* mammalian target of rapamycin 1, *ICG* indocyanine green, *SAG* superoxide anion generation, *Nrf2*, nuclear factor erythroid 2-related factor 2, *FeNa* fractional excretion of sodium, *NGAL* Lipocalin-2/neutrophil gelatinase associated lipocalin, *iNOS* inducible nitric oxide synthase, *eNOS* endothelial nitric oxide synthase, *MPO* Myeloperoxidase, *GFR* glomerular filtration rate, *Bcl-2* B-cell lymphoma 2, *ICAM-1* Intercellular Adhesion Molecule 1, *HSP-70* heat shock protein 70, *APAF-1* Apoptotic protease activating factor 1, *TBARS* thiobarbituric reactive species

Table 4 Renoprotective effect of PDE5I in Nephrotoxic nephropathy

Author, year	Study design	PDE5I/nephropathy Model	Nephrotoxic nephropathy	Renoprotective EFFEcts of PDE5I
Lee et al. 2009	Animal (Sprague–Dawley rats)	Sildenafil (0.4 mg/kg/day) Cisplatin-induced model	↑sCr, ↑BUN, ↑Caspase 3 expression, ↑Bax/Bcl-2 ratio, ↑TUNEL positive cells Loss of brush border, vacuolation and desquamation in renal tubular epithelium	↓sCr, ↓BUN, ↓Caspase 3 expression, ↓Bax/Bcl-2 ratio, ↓TUNEL positive cells Improved histological changes
Yang et al. 2010	Animal (Sprague–Dawley rats)	Udenafil (10 mg/kg) Cyclosporine A-induced model	↔ VEGF, ↓eNOS, ↑sCr, ↑BUN, Proximal tubule cell degeneration	↔ VEGF, ↑eNOS, ↓sCr, ↓BUN, Improved histological changes
Ali et al. 2011	Animal (Wistar Albino rats)	Sildenafil (0.5–10 mg/kg/day) Cisplatin-induced model	↑sCr, ↑BUN, ↑N-acetyl-β-D-glycosaminidase ↑TNF-α, ↑Renal platinum, ↓CrCl Tubular Necrosis, Apoptotic cells	↓sCr, ↓BUN, ↓N-acetyl-β-D-glycosaminidase ↓TNF-α, ↓Renal platinum, ↑CrCl Improved histological changes
Yang et al. 2013	Animal (Sprague–Dawley rats)	Udenafil (10 mg/kg) Cyclosporine A-induced model	↑sCr, ↓eNOS, ↑VEGF, ↑TUNEL positive cells ↓eNOS mRNA	↓sCr, ↑eNOS, ↓VEGF, ↓TUNEL positive cells ↑eNOS mRNA
Lauver et al. 2014	Animal (New Zealand white rabbits)	Sildenafil (6 mg/kg) CIN model	↑sCr, ↓Na, ↑K Tubular necrosis, Tubular degeneration	↓sCr, ↑Na, ↓K Improved histological changes
Zhu et al. 2014	Animal (Wistar Albino rats)	Tadalafil (10 mg/kg) E. colie induced renal damage	↑sCr, ↑BUN, ↑MDA, ↓SOD, ↑TGF-β, ↑NO ↑Systolic and diastolic BP,	↓sCr, ↓BUN, ↓MDA, ↑SOD, ↓TGF-β, ↓NO ↓Systolic and diastolic BP,
Essiz et al. 2014	Animal (Swiss Albino mice)	Vardenafil (30 mg/kg) Cyclosporine A-induced model	↓TAS levels, ↓tissue NO ↓COX-1, ↓COX-2,, ↓Pgp levels, ↓PDGF-A, ↓PDGF-C, ↓TGF-β1 ↑sCr, ↑BUN, ↑TOS levels	↑TAS levels, ↑tissue NO ↑COX-1, ↑COX-2, ↑Pgp levels, ↑PDGF-A, ↑PDGF-C, ↔TGF-β1, ↓sCr, ↓BUN, ↓TOS levels
Ma et al. 2015	Animal (BALB/c mice)	Icariin (30–60 mg/kg) Cisplatin-induced model	↓GSH, ↓Catalase, ↓SOD activity, ↓Bcl-2 ↑sCr, ↑BUN, ↑MDA, ↑TNF-α, ↑NF-Kβ ↑TUNEL positive cells, ↑cleaved caspase-3, Tubular necrosis, Inflammatory cell infiltration	↑GSH, ↑Catalase, ↑SOD activity, ↑Bcl-2 ↓sCr, ↓BUN, ↓MDA, ↓TNF-α, ↓NF-Kβ ↑TUNEL positive cells, ↓cleaved caspase-3, Improved histological changes(dose dependent)
Almeida et al. 2016	Animal (Wistar Albino rats)	Sildenafil (50 mg/kg/day) CIN model	↑sCr, ↑BUN, ↑urine protein, ↑RVR ↓GFR, ↑RPF, ↑superoxide anions production ↑H2O2 production ↑Peroxynitrite and hydroxyl Production	↓sCr, ↓BUN, ↓urine protein, ↓RVR ↑GFR, ↑RPF, ↔ superoxide anions production ↑H2O2 production ↑peroxynitrite and hydroxyl production
Benli et al. 2017	Animal (Wistar Albino rats)	Tadalafil (5–10 mg/kg) CLP model	↑sCr, ↑IL-6, ↑MPO, ↑MDA, ↑Cystatin C, ↓CAT, ↓SOD, Tubular injury, glomerular damage, Inflammatory cell infiltration	↓sCr, ↓IL-6, ↓MPO, ↓MDA, ↓Cystatin C, ↑CAT, ↑SOD, Improved histological changes
Khames et al. 2017	Animal (Sprague–Dawley rats)	Sildenafil (5 mg/kg/day) Doxorubicin-induced model	↑sCr, ↑Urea, ↑uric acid, ↑MDA, ↑TNF-α ↑caspase-3, ↓GSH, Tubular degeneration, vacuolization	↓sCr, ↓Urea, ↓uric acid, ↓MDA, ↓TNF-α ↓caspase-3, ↑GSH, Improved histological changes
Xie et al. 2018	Animal (C57BL/6 N mice)	Icariin (30–60 mg/kg) CLP model	↓Catalase, ↓GSH, ↓SOD, ↓Bcl-2 ↑sCr, ↑BUN, ↑MDA, ↑IL-1β/IL-6/TNF-α, ↑ NF- Kβ, ↑TUNEL positive cells, ↑Bax, ↑Caspase 3, ↑Renal vascular permeability Tubular necrosis	↑Catalase, ↑GSH, ↑SOD, ↑Bcl-2 ↓sCr, ↓BUN, ↓MDA, ↓IL-1β/IL-6/TNF-α, ↓ NF- Kβ, ↓TUNEL positive cells, ↓Bax, ↓Caspase 3, ↑Renal vascular permeability Improved histological changes
Iordache et al. 2019	Animal (Wistar Albino rats)	Tadalafil (5 mg/kg/day) Sildenafil (10 mg/kg/day) CIN model	↓TAC, ↓GSH, ↓CAT, ↑PROTC, ↑TBARS	↑TAC, ↑GSH, ↑CAT, ↓PROTC, ↓TBARS

Table 4 (continued)

Author, year	Study design	PDE5I/nephropathy Model	Nephrotoxic nephropathy	Renoprotective EFFEcts of PDE5I
Zhou et al. 2019	Human (Cell Culture)	Icariin (0.25–2.0 μM) Cisplatin-induced model	↓GSH, ↓Bcl-2, ↑p-NF-Kβ, ↑MDA, ↑Bax, ↑Caspase 3, ↑iNOS/TNF-α/IL-1β, ↑ROS ↑Apoptotic changes	↑GSH, ↑Bcl-2, ↓p-NF-Kβ, ↓MDA, ↓Bax, ↓Caspase 3, ↓iNOS/TNF-α/IL-1β, ↓ROS ↓Apoptotic changes

sCr serum creatinine, *BUN* Blood Urea Nitrogen, *SOD* superoxide dismutase, *TGF-β* transforming growth factor beta, *TNF-α* tumor necrosis factor α, *CrCl* Creatinine Clearance, *MCP-1* Monocyte chemoattractant protein-1, *ED-1* inflammation and monocyte/macrophage infiltration, *MDA* malondialdehyde, *NO* nitric oxide, *GSH* Glutathione, *CAT* catalase, *GPx* glutathione peroxidase, *TAS* total antioxidant status, *TOS* total oxidant status, *Urine 8-OH dG* urine. 8-hydroxy-2-deoxyguanosine, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *IL-1 β* Interleukin 1 beta, *AMPK* adenosine monophosphate-activated protein kinase, *mTORC1* mammalian target of rapamycin 1, *ICG* indocyanine green, *SAG* superoxide anion generation, *Nrf2*, nuclear factor erythroid 2-related factor 2, *FeNa* fractional excretion of sodium, *NGAL* Lipocalin-2/neutrophil gelatinase associated lipocalin, *iNOS* inducible nitric oxide synthase, *eNOS* endothelial nitric oxide synthase, *MPO* Myeloperoxidase, *GFR* glomerular filtration rate, *Bcl-2* B-cell lymphoma 2, *Bax* Bcl-2-associated X protein, *ICAM-1* Intercellular Adhesion Molecule 1, *HSP-70* heat shock protein 70, *APAF-1* Apoptotic protease activating factor 1, *TBARS* thiobarbituric reactive species, *RPF* renal plasma flow, *RVR* renal vascular resistance, *PROTC* protein carbonyl, *CLP* cecal ligation and puncture, *Pgp* P glycoprotein, *VGEF* Vascular endothelial growth factor, *NF- Kβ* nuclear factor kappa b, *PDGF* Platelet-derived growth factor, *ROS* reactive oxygen species, *TUNEL* terminal deoxynucleotidyl transferase dUTP nick end labeling, *CIN* contrast induced nephropathy

Further, 24 h pretreatment with the PDE5I icariin increased GSH level, decreased MDA and ROS levels, decreased Nuclear Factor kappa B (NF-κB) phosphorylation and nuclear translocation, and decreased IL-1β, TNF-α, and iNOS secretion in the human embryonic kidney (HEK) -293 cells, which had significantly improved oxidative stress following treatment with the anti-cancer chemotherapy drug, cisplatin [63]. It has been observed that when the PDE5I avanafil is administered for therapeutic purposes against dexamethasone-induced kidney damage, there are marked improvements in vitamin D3, bone morphogenetic protein 4 (BMP4), and BMP7 levels in kidney tissue [64]. Further, icariin treatment has been shown to significantly increase BUN and Cr levels, proinflammatory cytokine levels, oxidative damage, apoptosis, and vascular permeability in sepsis induced by cecal ligation and perforation (CLP) in a mouse model. Icariin decreased the expression of NF-B, caspase-3, and Bax, but increased the expression of Bcl-2, which is known to be involved in inflammation and apoptosis of the kidney [65]. It has also been shown that administration of icariin reduces cisplatin-induced oxidative stress, local inflammation, and tubular apoptosis, which have all been implicated in the pathogenesis of renal dysfunction. Icariin has been shown to have a protective effect by improving the expression of TNF-α, NF-κB, caspase-3, and Bcl-2 proteins in kidney tissue [66]. The administration of the PDE5I Udenafil significantly reduced tubular apoptosis, serum creatinine, and strong eNOS staining in CsA nephrotoxicity [67]. Taken together, these data indicate that PDE5I have a renoprotective effect in nephrotoxic nephropathy.

Renoprotective effect of PDE5 inhibitors in chronic kidney disease

Inflammation, oxidative stress, and apoptosis are the mechanisms that are held responsible for the pathophysiology and complications of CKD [68]. These pathophysiological changes are major mediators of CKD in both humans and animals and have been shown to cause similar effects in different rodent CKD models [69]. Animal models of CKD are essential for elucidating the underlying physiological, biochemical, and histopathological processes associated with CKD, as well as for the development and testing of potential therapeutic agents [70].

Results of studies investigating the effects of PDE5 inhibitors on CKD are presented in Table 5. The PDE5I Sildenafil prevents glomerular hypertension and hyperfiltration, and decreases high serum creatinine concentration and protein excretion in rats with subtotal nephrectomy [71]. In another animal model of CKD, while adenine induced kidney injury, sildenafil administration improved body weight, increased urea and Cr levels, increased the activities of NGAL and N-acetyl-β-D-glucosaminidase, and increased inflammatory

Table 5 Renoprotective effect of PDE5I in chronic kidney disease

Author, year	Study design	PDE5I/CKD model	Chronic kidney disease	Renoprotective effects of PDE5I
Tapia et al. 2012	Animal (Wistar Albino rats)	Sildenafil (5 mg/kg/day) 5/6 nephrectomy	↓NO2/NO3, ↓cGMP (urine), ↑proteinuria, ↑nitrotyrosine, ↑kidney hypertrophy	↑NO2/NO3, ↑cGMP (urine), ↓proteinuria, ↓nitrotyrosine, ↓kidney hypertrophy
Ali et al. 2018	Animal (Sprague–Dawley rats)	Sildenafil (0.1, 0.5, 2.5 mg/kg) Adenine	↓CrCl in urine, ↓osmolality, ↓CAT, ↓SOD, ↓TAS, ↓glutathione reductase, ↓sclerostin ↑adiponectin, ↑cystatin-C, ↑MDA, ↑NGAL, ↑Albumin, ↑sCr, ↑BUN, ↑total NO, ↑MAPK, ↑Caspase 3 positive cells, ↑TNF-α Fibrosis, mononuclear infiltration, tubular necrosis, tubular cast formation, necrotic nuclei, tubular cells apoptosis	↓CrCl in urine, ↑osmolality, ↑CAT, ↑SOD, ↑TAS, ↓glutathione reductase, ↑sclerostin ↓adiponectin, ↓cystatin-C, ↓MDA, ↓NGAL, ↓albumin, ↓sCr, ↓BUN, ↓total NO, ↓MAPK, ↓Caspase 3 positive cells, ↓TNF-α Improved histological changes

sCr serum creatinine, *BUN* Blood Urea Nitrogen, *SOD* superoxide dismutase, *MDA* malondialdehyde, *CAT* catalase, *MAPK* mitogen-activated protein kinase, *NGAL* Lipocalin-2/neutrophil gelatinase-associated lipocalin, *TNF-α* tumor necrosis factor α, *TAS* total antioxidant status, *CrCl* Creatinine Clearance, *NO*, nitric oxide, *cGMP* cyclic guanosine monophosphate

cytokines and antioxidant damage indices [72]. In the CKD model created with the 5/6 nephrectomy procedure, treatment with the PDE5I icariin revealed a protective effect on BUN, Cr, uric acid, TGF-β1, Hepatocyte growth factor (HGF), BMP-7, Wilms' tumour 1 (WT-1), and Pax2 levels. Moreover, icariin significantly increased the expression of CD133, CD24, odd-skipped related transcription factor 1 (Osr1), and Nanog, and increased the number of $CD133^+$ / $CD24^+$ renal stem/progenitor cells in kidney tissue [73]. In the kidneys of mice undergoing unilateral ureteral obstruction (UUO), there were significantly increased levels of profibrotic factors (TGF and connective tissue growth factor) and fibrotic markers (α-smooth muscle actin and fibronectin), pathological changes, and collagen deposition, all of which were significantly reversed with icariin treatment. Icariin treatment also significantly reduced the protein expression of proinflammatory factors and increased the protein expression of antioxidative enzymes (e.g., SOD and CAT) in the kidneys of UUO mice. Icariin treatment protects against renal fibrosis associated with CKD, thanks to its antifibrotic and anti-inflammatory properties [74]. Taken together, these data indicate that PDE5Is have a strong renoprotective effect against CKD.

Side-effects of PDE5I and future perspective

Most of the side effects associated with PDE5 inhibitors occur due to cross-reactivity with other PDE isoenzymes. These effects are usually dose dependent. Some of the common side effects encountered with the administration of PDE5Is are: mild headache, flushing, dyspepsia, back pain and myalgias, hypotension and dizziness, rhinitis, and mild and temporary loss of vision. However, side effects that are less common and can be considered more serious than other side effects; non-arteritic anterior ischemic optic neuropathy, hearing loss, priapism and melanoma [75].

Although isolated cardiovascular events and sudden deaths were reported in early studies with PDE5i, later studies have shown that this drug class does not have a greater risk than placebo [76]. However, it should be used with caution in cardiovascular diseases. Since the harmful effects of PDE5Is arise as a result of their use with nitrate or nitroglycerin, their use of cardiovascular drugs, especially nitrate ester drugs, is contraindicated [77]. In addition, Vardenafil causes the lenghtening of QT and is therefore known to be contraindicated in inpatients with type 1A, type 3 antiarrhythmics and congenital prolonged QT syndrome [75]. In addition, caution should be exercised in patients who need to be taken with alpha blockers, with a history of myocardial infarction in the last six months, stroke or life-threatening arrhythmia, resting hypotension or hypertension, history of heart failure or unstable angina [75].

While investigating the ability of PDE5Is to treat hypertension and angina, they were found to inadvertently cause an erection of the penis. PDE5I has been used to treat ED ever since. In addition, they are also used in the treatment of idiopathic pulmonary hypertension and premature ejaculation [75]. In addition to these diseases used in the clinic, positive results of preclinical studies have been published in many areas such as cardiovascular diseases, cancer, diabetes and urological problems. As reviewed above, promising results have been obtained in preclinical

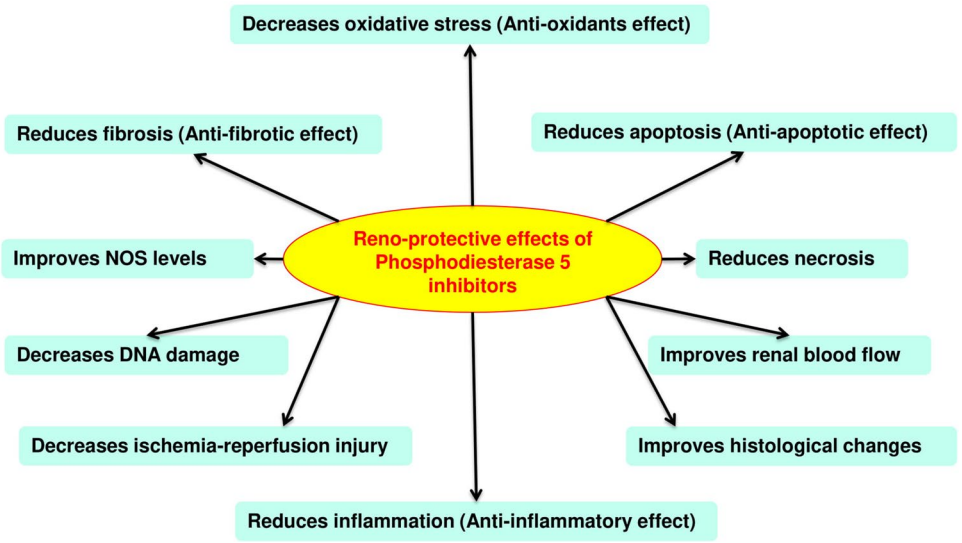

Fig. 2 Reno-protective effects of PDE5Is

studies with PDE5Is in renal diseases. However, since the results are obtained from animal studies, they need to be confirmed by clinical studies. Although many clinical studies focusing on potential cardiovascular benefits with PDE5Is (Clinical Trials.gov) have been described, there are not enough clinical studies on kidney diseases [78]. The number of clinical studies should be increased as soon as possible for PDE5Is to be used in the treatment of kidney diseases since the results of precilinic studies are positive and their possible side effects are low.

Conclusions

PDE5Is appear to be beneficial in renal diseases. They improve renal function and histopathological changes through a variety of mechanisms, including antioxidative, anti-inflammatory, anti-apoptotic, antifibrotic, and regional hemodynamic effects (Fig. 2). Regardless of the type of renal damage and the agent administered, the reno-protective effect of PDE5Is was observed in the vast majority of studies. The results of animal studies are promising, although the data are still limited. The potential reno-protective capacity of PDE5Is should be supported by further animal and clinical studies.

Declarations

Conflict of interest The authors have declared that no conflict of interest exists.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Informed consent was not required, as this study did not involve human participants.

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