International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 17, Issue 1, 2025

Original Article

PREVENTING DIABETIC KIDNEY DISEASE: A SYSTEMATIC REVIEW OF CURRENT PHARMACOLOGICAL APPROACHES

B. DHARANI*, STEPHY SEBASTIAN, S. NAZRIN, SUBA A.

[1*]A. C. S. Medical College and Hospital, Dr. M. G. R. Educational and Research Institute, Chennai, India
*Corresponding author: B. Dharani; *Email: doctordharanibhaskaran@gmail.com

Received: 17 Oct 2024, Revised and Accepted: 05 Dec 2024

ABSTRACT

Objective: This review examines the growing global burden of Diabetic Nephropathy (DN), a major complication of Diabetes Mellitus (DM) and a leading cause of Chronic Kidney Disease (CKD) and End-Stage Renal Disease (ESRD). With diabetes rates increasing, DN presents a significant health challenge. Current treatments manage established DN, but preventive strategies targeting high-risk individuals are urgently needed. This review evaluates current and emerging therapies for DN prevention.

Methods: A comprehensive literature search was conducted across multiple databases (PubMed, Web of Science, SCOPUS and others) to identify studies on the treatment and prevention of DN in DM patients. Eligible studies included Randomized Controlled Trials (RCT), cohort studies and meta-analyses published upto 2024, focusing on outcomes like albuminuria, Glomerular Filtration Rate (GFR) and ESRD incidence.

Results: Current treatments, including Sodium Glucose Co-transporter 2 (SGLT2) inhibitors, Angiotensin-Converting Enzyme (ACE) inhibitors and Angiotensin Receptor Blocker (ARB), effectively reduce albuminuria and slow progression. Emerging therapies, such as antioxidants (*Alpha-Lipoic Acid* (*ALA*), *Resveratrol*), Mineralocorticoid Receptor Antagonists (MRA) and Endothelin Receptor Antagonists (ERA), show promise in improving kidney function and reducing inflammation. Other potential therapies targeting Oxidative Stress (OS), inflammation and fibrosis, such as Advanced Glycation End products(AGE) inhibitors and Tumor Necrosis Factor-α (TNF-α) inhibitors, have demonstrated preclinical efficacy but require further validation.

Conclusion: While current therapies slow DN progression, they do not offer definitive prevention. Emerging treatments targeting oxidative stress, inflammation and fibrosis show promise in reducing kidney damage. However, challenges like side effects and long-term safety remain. Further research is needed to establish the efficacy of these therapies and develop personalized strategies for preventing DN in high-risk populations.

Keywords: Diabetic kidney disease, Diabetic nephropathy, DN, DKD, Preventive therapy, Preventing diabetic nephropathy, Preventing DKD, Diabetes complications

DOI: https://dx.doi.org/10.22159/ijap.2025v17i1.52956 Journal homepage: https://innovareacademics.in/journals/index.php/ijap

INTRODUCTION

Diabetes mellitus (DM) is a global metabolic disorder with a rapidly increasing incidence, rising from 108 million cases in 1980 to 451 million in 2017 and projected to affect 693 million people by 2045 [1, 2]. This alarming trend presents a major healthcare challenge worldwide. Among the chronic complications of DM, Diabetic Nephropathy (DN) is one of the most serious and feared. Affecting approximately 40% of individuals with diabetes, DN significantly contributes to the burden of Chronic Kidney Disease (CKD) and End-Stage Renal Disease (ESRD), making diabetes the leading cause of ESRD globally [3]. Cardiovascular complications also present a major concern for individuals with DN, with cardiovascular disease being the primary competing risk before patients reach stage 4 CKD [4].

DN is a long-term, progressive kidney condition that typically manifests after 10 to 20 years of diabetes, initially characterized by microalbuminuria and progressing to macroalbuminuria and eventual renal impairment [5, 6]. Early intervention is crucial, as strict control of blood glucose and Blood Pressure (BP) has been shown to slow disease progression [7]. However, despite advances in treatment, including the use of ACE Inhibitors (ACEI), Angiotensin II Receptor Blockers (ARB) and newer therapies like Sodium Glucose co-Transporter (SGLT2) inhibitors, the majority of current interventions focus on managing the condition after it has already developed rather than preventing its onset.

This presents a critical gap in diabetes care. While existing therapies help control blood glucose and mitigate renal and cardiovascular complications, there is a pressing need for preventive strategies that can specifically target high-risk diabetic individuals before DN develops. Identifying and developing preventive therapies is essential to reduce the incidence of DN, ESRD and the need for Renal Replacement Therapy (RRT). By shifting focus toward early prevention, we can significantly improve patient outcomes, reduce healthcare costs and alleviate the growing burden of diabetes-related kidney disease. This review will explore the current landscape of drug treatments for DN and examine emerging preventive approaches that could transform the management of Diabetic Kidney Disease (DKD).

MATERIALS AND METHODS

Literature search strategy

A comprehensive literature search was performed to identify relevant studies examining treatment and preventive strategies for DN and DKD in individuals with DM. The search was conducted in multiple electronic databases, including Springer, Wiley, Web of Science, PubMed, Google Scholar, SCOPUS, Embase and Cochrane Library, with no restriction on publication date up to 2024. To further enhance the breadth of the review, references cited within included articles were also manually searched.

The following keywords and Boolean operators were used in the search: "Diabetic Nephropathy" OR "Diabetic Kidney Disease", "Diabetes Mellitus" AND "Treatment" OR "Prevention", "SGLT2 inhibitors" OR "ACE inhibitors" OR "Angiotensin Receptor Blockers", "Investigational drugs to prevent Diabetic Kidney disease", "Investigational drugs to prevent Nephropathy". The search strategy was refined using these terms in combination to ensure inclusion of studies relevant to both the treatment and prevention of DN/DKD.

Inclusion and exclusion criteria

Articles were considered for inclusion if they met the following criteria: Published in peer-reviewed journals, investigated the treatment or prevention of DN/DKD in patients with Type 1 Diabetes Mellitus (T1DM) or Type 2 Diabetes Mellitus (T2DM), reported clinical outcomes related to albuminuria, Glomerular Filtration Rate (GFR) or the incidence of ESRD, involved Randomized

Controlled Trials (RCT), cohort studies or meta-analyses and published between 2000 and 2024.

Studies were excluded if: They focused on non-diabetic kidney disease, the population consisted exclusively of patients without diabetes, they did not report relevant outcomes for DN/DKD or lacked sufficient clinical data, they were not published in peer-reviewed journals (e. g., conference abstracts) and the full text was unavailable or did not provide usable data for analysis.

Data extraction and evaluation

Data from the included studies were extracted and evaluated based on the quality of the evidence and the relevance of the findings. Key variables extracted included study design, patient population, type of intervention or preventive measure, outcomes related to renal function (e.g., albuminuria progression, GFR) and any reported adverse events.

Risk of bias assessment

The risk of bias for each included study was assessed using the Cochrane Risk of Bias Tool for RCT and the Newcastle-Ottawa Scale for observational studies. Bias was evaluated across several domains: Selection bias (e.g., random sequence generation, allocation concealment), Performance bias (e.g., blinding of participants and personnel), Detection bias (e.g., blinding of outcome assessment), Reporting bias (e.g., selective reporting of outcomes).

Studies were categorized as having low, moderate or high risk of bias in each domain. Any disagreements regarding bias assessments were resolved through discussion among the authors. Sensitivity analyses were conducted to assess the robustness of the review findings, especially in studies with a high risk of bias.

RESULTS AND DISCUSSION

Pathophysiology of DKD

The mechanisms underlying DKD arise from the interplay of three primary processes: hemodynamic, metabolic, and inflammatory factors. Each process contributes differently depending on an individual's genetic background, which explains variability in disease progression.

Hemodynamic factors

A crucial element of the hemodynamic aspect of DKD is the Renin-Angiotensin-Aldosterone System (RAAS). Renin, secreted by juxtaglomerular cells near the afferent arterioles, is pivotal for RAAS activation. Angiotensin II, produced through this pathway, binds to AT1 and AT2 receptors: AT1 receptor activation leads to increased resistance in efferent arterioles and elevated intraglomerular pressure maintaining renal filtration rates and AT2 receptor activation promotes vasodilatory Prostaglandin (PG) release, which offers a protective counterbalance [8].

Elevated angiotensin II levels contribute to renal injury through non-hemodynamic mechanisms: Stimulates aldosterone secretion and Promotes release of inflammatory chemokines, such as MCP-1 and TGF-β [9, 10].

Metabolic factors

Hyperglycemia, Insulin Resistance (IR) and dyslipidemia contribute to the progression of DKD. Excess glucose load in the proximal tubule upregulates SGLT-1 and SGLT-2, enhancing glucose and sodium reabsorption. This leads to decreased sodium delivery to the distal nephron and impaired tubuloglomerular feedback, disrupting normal glomerular hemodynamics [11-13].

Local factors

Factors like Endothelin-1, Reactive Oxygen Species (ROS) and Thromboxane A2 (TXA2) increase the tone of efferent arterioles contributing to glomerular hypertension. IR increases the production of Cyclooxygenase-2 (COX-2), prostanoids and the kallikrein-kinin system, resulting in the dilation of the afferent arterioles.

Activation of the Renin-Angiotensin System (RAS) can damage Glomerular Endothelial Cells (GEC), increasing fenestrations and triggering apoptosis. Hyperglycemia promotes the formation of Advanced Glycation End products (AGE), which attach to their RAGE receptors that reduces Nitric Oxide (NO) availability and increase activity of Transforming Growth Factor-Beta (TGF-β), a fibrotic factor. Diabetes accelerates the aging of Endothelial Progenitor Cells (EPC), diminishing their reparative capabilities.

Podocyte dysfunction

Podocytes exhibit dysregulated production of Vascular Endothelial Growth Factor (VEGF). Damage to podocytes results in foot process effacement and podocyte loss, which is a key mechanism in the development of albuminuria in diabetic patients [14-17].

Inflammation and fibrosis

Inflammation and fibrosis play crucial roles in the development of DKD. Infiltration of renal tissue by macrophage is a significant characteristic of DKD. Hyperglycemia and angiotensin II contribute to the recruitment of macrophages, which amplify inflammation through cytokine release. Activation of Mineralocorticoid Receptors (MR) intensifies the inflammatory response and contributes to glomerular damage by promoting sodium reabsorption and potassium excretion [18-20].

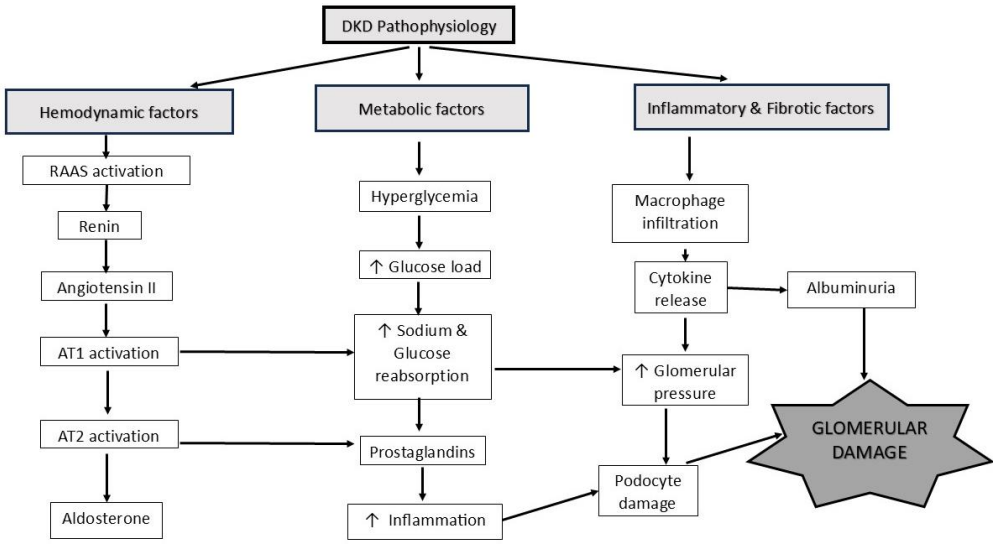

Fig. 1: Pathophysiology of DKD

Drugs to prevent DKD

Preventing DKD involves a multifaceted approach aimed at managing the underlying risk factors associated with diabetes. First and foremost, maintaining tight blood glucose control through diet, exercise and medications is essential to prevent damage to the kidneys. Monitoring and managing BP is equally critical, as high BP can accelerate kidney damage. Keeping BP within target levels (typically<130/80 mm Hg) through lifestyle changes and medications like ACE inhibitors or ARB is recommended. Reducing excess weight, avoiding smoking and limiting alcohol intake are also key lifestyle modifications that improve overall kidney health. Additionally, controlling cholesterol levels with statins can help reduce the cardiovascular risk that often accompanies diabetes and contributes to kidney dysfunction. Regular screening for early signs of kidney damage, such as albuminuria (protein in the urine) allows for early intervention and monitoring. In some cases, medications like SGLT2 inhibitors may be prescribed to further protect the kidneys. By addressing these modifiable risk factors along with a focus on diet, exercise and regular medical check-ups, individuals with diabetes can significantly reduce their risk of developing diabetic kidney disease.

Current treatment options

Glycemic control

Glycemic control is fundamental in managing DKD. The American Diabetes Association (ADA) recommends an A1C target of<7% for most adults with diabetes, while the American College of Physicians (ACP) suggests a target range of 7-8% for patients with long-standing diabetes or limited life expectancy [21, 22]. Studies show that aggressive glycemic control (e.g., A1C<6%) can reduce DKD incidence, but it may increase the risk of hypoglycemia, especially in older adults or those with cardiovascular disease [23]. Therefore, treatment should be individualized based on the patient's risk profile.

DPP-4 Inhibitors (e.g., *Sitagliptin, Saxagliptin*) reduce albuminuria independently of glucose control and are generally well tolerated. However, they may increase the risk of Heart Failure (HF) and have uncertain long-term benefits in preventing ESRD [24-26].

GLP-1 Receptor Agonists (e.g., *Semaglutide*, *Liraglutide*) protect renal endothelial cells and reduce Oxidative Stress (OS), improving kidney function and albuminuria. However, gastrointestinal side effects and risks of pancreatitis may limit their use [27-29].

SGLT2 Inhibitors (e.g., *Empagliflozin*, *Canagliflozin*) are a breakthrough in DKD management, significantly reducing renal disease progression and the need for RRT, as shown in the EMPA-REG OUTCOME trial [30, 31]. They can cause urinary and genital infections and dehydration and their long-term renal benefits in broader populations are still under study.

Thiazolidinediones (e.g., *Pioglitazone*) can reduce albuminuria but are limited by side effects such as weight gain and edema, with unclear benefits in preventing ESRD [32].

BP control

Control of BP is crucial in preventing the progression of DKD. While a target BP of<140/90 mm Hg is generally recommended, achieving this may not be appropriate for all patients [33, 34].

ACE Inhibitors (e.g., *Enalapril*, *Ramipril*) are effective in reducing albuminuria and mortality in DKD but can cause hyperkalemia, hypotension and renal impairment, especially in patients with existing kidney dysfunction [35, 36].

Aldosterone Antagonists (e.g., *Spironolactone*) lower proteinuria and BP, particularly in patients already on ACE inhibitors or ARB. However, they carry risks of hyperkalemia and gynecomastia and their benefit in advanced DKD remains unclear [37, 38].

ARB (e. g., *Losartan*, *Valsartan*) also reduce albuminuria and slow DKD progression. Like ACE inhibitors, they can cause hyperkalemia and hypotension and their long-term efficacy in advanced CKD is still under investigation [39].

MRA such as *Spironolactone*, *Eplerenone* and nonsteroidal MRAs like *Finerenone* have shown promise in reducing albuminuria and improving renal outcomes in DKD. Nonsteroidal MRAs, including *Finerenone* have a lower incidence of hyperkalemia and may offer a safer alternative to traditional therapies. Similarly, *esaxerenone* and *KBP-5074*, other nonsteroidal MRAs have also been found to significantly reduce Urine Albumin to Creatinine Ratio (UACR) in patients with diabetes and CKD [40-53]. These agents, especially when combined with ACE inhibitors or ARB, provide cardiorenal protection, though potassium monitoring is essential.

Table 1: Current treatment options to prevent DKD

Drug category	Drug	Mechanism of action	Dose	Side effects	Cost	Reference number
Glycemic control	DPP-4 Inhibitors	Inhibit DPP-4, increasing incretin hormones, improving insulin secretion, and reducing albuminuria	*Sitagliptin* (100 mg daily), *Saxagliptin* (5 mg daily)	Nasopharyngitis, heart failure risk, hypoglycemia (rare)	Moderate	[24-26]
	GLP-1 Receptor Agonists	Increase insulin secretion, decrease glucagon secretion, and reduce renal oxidative stress, improving albuminuria	Semaglutide (0.25 mg weekly), Liraglutide (0.6 mg daily)	Nausea, vomiting, pancreatitis risk, Hypoglycemia	High	[27-29]
	SGLT2 Inhibitors	Block sodium-glucose cotransporter 2 (SGLT2), reducing glucose reabsorption in the kidney, improving albuminuria, and slowing renal disease progression	*Empagliflozin* (10 mg daily), *Canagliflozin* (100 mg daily)	UTIs,Mycotic genital infections, dehydration, DKA (rare)	High	[30, 31]
	Thiazolidinediones	Activate PPAR-γ receptors, improving insulin sensitivity and reducing albuminuria	*Pioglitazone* (15-45 mg daily)	Weight gain, edema, heart failure risk	Moderate	[32]
BP control	ACE Inhibitors	Inhibit angiotensin-converting enzyme, reducing aldosterone, promoting vasodilation, and lowering proteinuria	*Enalapril* (5-40 mg daily), *Ramipril* (2.5-10 mg daily)	Hyperkalemia, hypotension, Cough, Increase serum creatinine level, Teratogenicity	Low	[35, 36]
	Aldosterone Antagonists	Block aldosterone receptors, reducing sodium retention, proteinuria, and BP	*Spironolactone* (25-100 mg daily)	Hyperkalemia, gynecomastia	Low	[37, 38]
	ARB	Block angiotensin II receptors, reducing vasoconstriction and aldosterone release, improving albuminuria	*Losartan* (25-100 mg daily), *Valsartan* (40-160 mg daily)	Hyperkalemia, hypotension, Increase in serum creatinine	Moderate	[39]
	MRA	Block mineralocorticoid receptors, reducing proteinuria, blood pressure, and kidney damage	*Spironolactone* (25-100 mg daily), *Finerenone* (10-20 mg daily)	Hyperkalemia, hyponatremina, gynecomastia, hypovolemia (*Spironolactone*)	High	[40-53]

Critical analysis

Despite the availability of various pharmacological agents to control glycemia and blood pressure in DKD, several key limitations remain. First, while ACE inhibitors, ARB and SGLT2 inhibitors have demonstrated efficacy in slowing the progression of renal disease, none of these therapies are curative. They predominantly serve as disease-modifying agents, with benefits primarily in reducing albuminuria and delaying the progression to more severe stages of DKD. However, in many patients, particularly those with advanced disease these agents provide only limited protection.

Furthermore, side effects are a significant concern. ACE inhibitors and ARBs may cause hyperkalemia and renal dysfunction, while SGLT2 inhibitors increase the risk of urinary and genital infections. Thiazolidinediones, while effective in some cases, can exacerbate heart failure, weight gain and edema, limiting their use in certain patient populations.

As a result, there is an urgent need for individualized treatment approaches in managing DKD. Treatment regimens should be tailored to the patient's specific stage of disease, comorbid conditions and risk factors. A more personalized approach incorporating factors such as age, underlying cardiovascular risk and co-morbidities may optimize therapeutic outcomes and minimize adverse effects.

Experimental treatment

Antioxidants

Alpha-lipoic acid (ALA)

A potent antioxidant that neutralizes ROS and reduces OS, *ALA* protects against DKD. It improves renal function, reduces fibrosis and decreases inflammatory cytokines (IL-6, TNF-α) by modulating pathways like p38 MAPK and NF-κB [54-56]. Clinical trials show *ALA* reduces urinary albumin excretion, a key marker of kidney dysfunction in diabetes. Typical dosages range from 600–1,200 mg/day [57-59].

Resveratrol

This polyphenol regulates oxidative stress, inflammation and autophagy in DN. It reduces ROS, enhances antioxidant defenses and improves kidney function through the AMPK/SIRT1/Nrf2 and Keap1/Nrf2 pathways [60, 61]. Studies show it also reduces proteinuria and improves renal structure [62, 63]. Combined with other treatments, *Resveratrol* may enhance DN management [64]. Network pharmacology highlights therapeutic targets for *Resveratrol* in DKD [65].

Curcumin

Known for anti-inflammatory, antioxidant and anti-apoptotic effects, curcumin protects the kidneys by activating Nrf2 and inhibiting NF-κB. It reduces OS, inflammation and fibrosis, particularly in DN [66-70]. *Curcumin* nanoparticles (nCUR) have shown promise in delaying DKD progression, even without controlling hyperglycemia [71]. It also modulates inflammation in CKD patients [72-75].

Sulbutiamine

It is a synthetic vitamin B1 derivative. *Sulbutiamine* reduces OS, improves kidney function and suppresses inflammatory markers in DN models [76].

Schisandrin B (Sch B)

It isa plant-derived lignan that targets mitochondrial dysfunction and Epithelial-Mesenchymal Transition (EMT) in renal tubular cells, reducing fibrosis and improving mitochondrial function in DKD. *Sch B* acts through the TGF-β1, PI3K/Akt, and AMPK pathways [77].

AGE formation inhibitors

Diphlorethohydroxycarmalol (*DPHC*) is found in brown seaweed. *DPHC* inhibits the AGE-RAGE interaction, preventing MGO-induced renal damage and regulating apoptosis [78]. Other AGE inhibitors like *Aminoguanidine* show promise, although clinical trials have been limited due to side effects [79-81].

Aldose reductase inhibitors (ARIs)

*WJ-39*and*Epalrestat*are ARI that inhibit the polyol pathway to protect against diabetic kidney damage. *WJ-39* improves mitochondrial function and reduces fibrosis in preclinical models [82]. *Epalrestat* has beneficial effects on renal function and interacts with key pathways (AGE-RAGE, TNF, HIF-1) [83], though gastrointestinal side effects limit its clinical use.

MRA

Esaxerenone is an MR blocker. *Esaxerenone* reduces albuminuria in DN independent of BP-lowering effects [84].

Endothelin-1 receptor A (ETA) antagonists

Atrasentan and *Zibotentan* are ETA-selective antagonists that reduce glomerular permeability and proteinuria, showing potential for DN and CKD. *Atrasentan* has shown promise in reducing renal events and albuminuria [85-91]. However, side effects like fluid retention and hepatotoxicity are concerns with long-term use.

mTOR inhibitors

mTOR signaling, activated by high glucose and cytokines in diabetes, promotes cell proliferation and fibrosis in kidney cells, contributing to DKD. mTOR activation impairs autophagy and promotes OS, inflammation and podocyte damage. *Rapamycin*, an mTOR inhibitor, shows promise in preclinical models but has side effects, including proteinuria and IR [92-105]. Other mTOR-targeting agents, like thiazolidinediones (*Rosiglitazone*), aldosterone antagonists (*Spironolactone*) and plant compounds (e.g., *Tripterygium glycoside*), show protective effects in DKD [106-114]. Vitamin D Receptor (VDR) activation, through DDIT4 upregulation, inhibits mTOR, mitigating kidney injury and fibrosis. These findings support mTOR inhibition as a potential DKD therapy, though further research is needed [115-121].

TNF-α inhibitors

TNF-α and its receptors, TNFR1 and TNFR2, play a role in the progression of DKD. Inhibiting TNF activity in diabetic models reduces proteinuria, sodium retention and kidney hypertrophy. Soluble TNF receptors like TNFR: Fc and *Etanercept* show promise in mitigating renal damage, suggesting TNFR as a key therapeutic target in DKD [122-126].

Pentoxifylline (PTX)

PTX has shown benefits in DKD by reducing proteinuria, improving kidney function (creatinine clearance), controlling inflammation and OS. *PTX* also improves lipid profiles, lowering LDL-C and Triglycerides (TGL) and reduces TNF-α levels. These multifactorial effects underscore its potential in DKD management [127-134]. Large-scale studies are needed to confirm *PTX*'s therapeutic potential.

Protein kinase C inhibitors (PKCI)

PKC β overactivity contributes to DN via collagen production and fibrosis. *Ruboxistaurin*, a selective PKC β inhibitor, reduces glomerular hyperfiltration and proteinuria in diabetic rats [135, 136]. *Echinochrome A* (*EchA*), derived from sea urchins, also inhibits PKC and improves renal function in diabetic models by reducing OS and fibrosis [137].

Nox1/4 inhibitors

NOX1 and NOX4 enzymes generate ROS, promoting inflammation and fibrosis in DKD. *GKT137831*, a dual NOX1/4 inhibitor, shows protective effects in preclinical DN models. The NOX-E36 inhibitor reduced albuminuria in DN patients, suggesting its potential for preventing kidney damage [138-140].

Nrf2 activators

Nrf2 activation enhances antioxidant capacity, reduces inflammation and prevents fibrosis, critical in DN. *Bardoxolone Methyl*, an Nrf2 activator, improved GFR in diabetic patients, though cardiovascular concerns led to trial termination [141, 142].

Table 2: Experimental treatment to prevent DKD

Drug category	Drug	Mechanism of action	Study model	Study outcome	Challenges in development	Reference number	Why it can be used in preventing DKD?
Antioxidants	*ALA*	Neutralizes ROS, reduces OS, modulates inflammatory and fibrotic pathways	Animal (Preclinical), Human (Clinical)	Preclinical studies showed protective effects on kidney function, reduced hyperglycemia, prevented glomerulosclerosis and fibrosis. Clinical trials showed decreased albumin excretion.	Mild side effects (GI discomfort, hypoglycemia), optimal dosage and long-term safety need further study	[54-59]	OS is a key driver of DKD and *ALA* targets this pathway, offering potential for kidney protection.
	Resveratrol	Modulates AMPK/SIRT1/Nrf2 and Keap1/Nrf2 pathways, reduces ROS, enhances antioxidant enzymes, improves kidney function.	Animal (Preclinical), Human (Clinical)	Reduced proteinuria, improved kidney structure, decreased inflammatory markers. Subgroup analyses showed beneficial effects with or without co-treatment with other medications.	Long-term efficacy and optimal dosage still under investigation.	[60-65]	Given the role of inflammation and oxidative stress in DKD, resveratrol could help reduce these factors, slowing kidney damage.
	Curcumin	Reduces OS, prevents renal damage, enhances mitochondrial function, modulates Nrf2 and NF-κB.	Animal (Preclinical), Human (Clinical)	Reduced renal inflammation and fibrosis, improved kidney function in diabetic rat models. In human trials, reduced inflammation in CKD patients.	More research needed for precise mechanisms and clinical application.	[62-66, 103-106]	*Curcumin* offers antioxidant, anti-inflammatory, and antifibrotic properties, essential for combating DKD progression.
	Sulbutiamine	Reduces OS, suppresses inflammatory markers, improves kidney function.	Animal (Preclinical)	Reduced fasting blood glucose, improved kidney function (decreased urea, creatinine), reduced inflammation, and improved histopathological changes in kidneys of diabetic rats.	Limited human data on long-term effects.	[76]	Targets OS and inflammation, core contributors to DKD, with promising effects in early studies.
	Sch B	Inhibits EMT, improves mitochondrial function, reduces ROS, enhances ATP production.	Animal (Preclinical)	Prevented EMT in renal tubular cells, improved mitochondrial function, reduced fibrosis and OS.	Limited human studies and clinical validation.	[77]	Inhibiting EMT and improving mitochondrial function may help prevent fibrosis and functional decline in DKD.
AGE formation inhibitors	*DPHC*	Inhibits AGE-RAGE interaction, regulates apoptosis, enhances Nrf2 pathway.	Animal (Preclinical)	Prevented AGE-related kidney damage, suppressed RAGE protein expression, reduced renal damage in diabetic rats.	Limited clinical data, need for larger trials.	[78]	AGE accumulation accelerates DKD progression; targeting AGE-RAGE interactions may slow down this process.
	Aminoguanidine	Inhibits AGE formation by trapping reactive carbonyl compounds and preventing glycoxidation.	Animal (Preclinical), Human (Clinical)	Reduced renal AGE accumulation and mesangial expansion in diabetic rats, but minimal benefits in human trials for overt nephropathy	Discontinued due to toxicity and adverse effects in humans.	[79-81]	AGEs contribute to fibrosis and inflammation in DKD, making their inhibition crucial for slowing disease progression.
Aldose Reductase Inhibitors (ARIs)	*WJ-39*	Inhibits aldose reductase, reducing polyol pathway activation, improves mitochondrial function, reduces fibrosis.	Animal (Preclinical)	Protected against renal tubular damage in diabetic rats, improved mitochondrial function and reduced fibrosis.	Long-term safety and efficacy in humans remain to be confirmed.	[82]	The polyol pathway is linked to DKD progression, and inhibition could reduce kidney damage and fibrosis.
	Epalrestat	Inhibits aldose reductase, reducing renal metabolic disturbances and inflammatory pathways.	Human (Clinical), Animal (Preclinical)	Reduced renal dysfunction and metabolic disturbances in DN patients, decreased inflammation.	Gastrointestinal side effects and liver enzyme abnormalities limit use.	[83]	Inhibition of aldose reductase could provide a direct therapeutic benefit in addressing metabolic disturbances in DKD.
MRA	*Esaxerenone*	Blocks MR, reduces albuminuria independent of BP reduction.	Human (Clinical)	Reduced Urine Albumin-to-Creatinine Ratio (UACR) in patients with DN, independent of BP effects.	Further research needed to clarify mechanisms and efficacy across different populations.	[84]	Blocking MR can reduce albuminuria, a key marker of kidney damage in DKD.
ETA	*Ambrisentan*, *Macitentan*, *Sitaxentan*, *BQ-123*,	Selective antagonism of ETA receptors, reducing vasoconstriction,	Preclinical, Clinical	Reduced glomerular permeability, lower BP, potential for treating resistant hypertension, DN	Side effects: hepatotoxicity, fluid retention, anemia, particularly with long-term	[85-91]	ETA can mitigate vasoconstriction and inflammation, both of which

Drug category	Drug	Mechanism of action	Study model	Study outcome	Challenges in development	Reference number	Why it can be used in preventing DKD?
	Darusentan, *Avosentan*, *Atrasentan*, *Zibotentan*	inflammation and renal damage			use of *Sitaxentan, Avosentan*		contribute to DKD progression.
	Bosentan, Tezosentan, Aprocitentan	Dual antagonism of ETA and ETB receptors, vasodilation, renal protection	Preclinical, Clinical	*Bosentan* approved for PAH; *Tezosentan* does not reduce cardiovascular events; *Aprocitentan* lowers BP in resistant hypertension	Liver dysfunction, fluid retention, lack of cardiovascular event reduction in clinical trials	[163-169]	Dual antagonism of endothelin receptors can help combat renal vasoconstriction and improve kidney outcomes in DKD.
mTOR Inhibitor	*Rapamycin*, Thiazolidinediones (e. g., *Rosiglitazone*), Aldosterone antagonists (e. g., *Spironolactone*)	Inhibition of mTOR signaling pathway, preventing podocyte damage and glomerular hypertrophy	Preclinical, Clinical	Reduced kidney injury, improved glomerular function, reduced fibrosis and inflammation	Side effects: proteinuria, renal tubular necrosis, insulin resistance, immune suppression	[92-105]	mTOR inhibitors can protect glomerular integrity and prevent kidney injury, crucial for preventing DKD.
	Tripterygium Glycoside, Triptolide, Radix Astragali, Paecilomyces Cicadidae, Dihydromyricetin, Ginsenoside Rg1, Kaempferol	Modulation of mTOR signaling, enhancing autophagy, reducing epithelial-mesenchymal transition and apoptosis	Preclinical, *In vitro*	Protection of renal function, delayed DKD progression, improved autophagic processes	Limited clinical data, potential safety concerns, unclear mechanisms of action	[106-114]	Modulating mTOR signaling could enhance kidney function and delay DKD progression by promoting autophagy and reducing fibrosis.
TNF-α Inhibitors	*Infliximab, Etanercept*	Inhibition of TNF signaling, reduction of inflammation, sodium retention and renal hypertrophy	Preclinical (STZ rats), Clinical (human)	Reduced urinary TNF excretion, attenuated kidney damage, decreased albuminuria	Limited understanding of TNFR1 vs TNFR2 contributions, variable outcomes across models	[122-126]	TNF-α is a major pro-inflammatory mediator in DKD; its inhibition could help reduce kidney inflammation and damage.
PTX	*PTX*	Anti-inflammatory, reduces oxidative stress, improves lipid profile and enhances kidney function	Clinical (human), Preclinical	Reduced UACR, improved creatinine clearance, reduced inflammation and OS	Need for large-scale, longitudinal studies to confirm findings, safety profile concerns	[127-134]	PTX's anti-inflammatory and antioxidant effects make it a potential therapy to reduce kidney damage in DKD patients.
PKCI	*Ruboxistaurin, EchA*	Inhibition of PKC β and downstream pathways, reducing fibrosis and oxidative stress	Preclinical (rat, mouse), Clinical	Reduced glomerular hyperfiltration, proteinuria, improved renal function in DN models	Limited human trials, efficacy and safety concerns, need for long-term data	[135-137]	PKC activation plays a role in DKD progression; inhibiting it could help reduce fibrosis and renal damage in diabetes.
Nox1/4 Inhibitor	*GKT137831, NOX-E36*	Inhibition of NOX1 and NOX4, reducing ROS production and kidney damage	Preclinical (mouse), Clinical (human)	Significant reduction in albuminuria, potential efficacy in preventing kidney damage	Lack of long-term clinical data, variable response across patient populations	[138-140]	NOX enzymes contribute to OS in DKD; inhibiting them may prevent kidney injury and slow disease progression.
Nrf2 Activator	*Bardoxolone Methyl*	Activation of Nrf2 pathway, enhancing antioxidant capacity and reducing inflammation	Clinical (human)	Increased glomerular filtration rate (GFR), but trial terminated early due to cardiovascular events	Safety concerns (cardiovascular risks), need for further trials to confirm long-term benefits	[141, 142]	Activating Nrf2 enhances kidney antioxidant defenses, which is critical in managing OS in DKD.
JAK-STAT Inhibitor	*Baricitinib*	Inhibits JAK1 and JAK2, suppresses inflammation and reduces albuminuria.	Phase II clinical trial in type 2 diabetic patients with DKD.	Significant reduction in albuminuria (40%), reduction in pro-inflammatory biomarkers (e. g., CXCL10, CCL2). Common AE: anemia.	Potential safety concerns with long-term use (e. g., anemia, infection). Further large-scale trials needed.	[143-154]	Shows promising results in reducing inflammation, albuminuria, and fibrosis in DKD patients.
	Ruxolitinib	It blocks JAK1 and JAK2, leading to a decrease in inflammation and fibrosis while also regulating podocyte autophagy.	Preclinical animal models (STZ-induced Wistar rats, HG-induced MPC-5 cell model).	Reduced proteinuria, decreased levels of inflammatory markers (TNF-α, TGF-β1, NF-κB), and fibrosis markers (vimentin).	No clinical trials yet for DKD, limited full animal studies.		Potential for reducing kidney fibrosis and inflammation in DKD, though further research needed.
	Nifuroxazide	Inhibits JAK2 and Tyk2, suppresses STAT3	Preclinical studies in STZ-induced SD rats,	Reduced oxidative stress, inflammation, and renal fibrosis.	Lack of clinical trials for DKD, but long-term safety		High oral safety promising anti-inflammatory and

Drug category	Drug	Mechanism of action	Study model	Study outcome	Challenges in development	Reference number	Why it can be used in preventing DKD?
		phosphorylation, reduces oxidative stress and inflammation.	UUO rats.	Improved glucose metabolism.	in clinical use suggests promise.		antioxidative effects could be useful in DKD treatment.
	Sinomenine	Inhibits JAK2/STAT3/SOCS1 pathway, reduces inflammation, fibrosis, and apoptosis.	Preclinical studies in STZ-induced SD rats.	Reduced apoptosis of renal cells, along with decreased inflammation and fibrosis. Skin lesions and gastrointestinal discomfort noted.	Potential side effects such as skin lesions and gastrointestinal issues.		Potential therapeutic option for inflammation and fibrosis in DKD through JAK/STAT modulation.
	Silymarin	It blocks the JAK2/STAT3/SOCS1 and TGF-β/Smad signaling pathways, leading to a reduction in inflammation, oxidative stress, and fibrosis.	Preclinical studies in STZ-induced SD rats.	Improved podocyte injury, reduced oxidative stress, and renal fibrosis. Gastrointestinal discomfort reported as AE.	Teratogenicity concerns in animal studies, limited clinical data.		May help reduce oxidative stress and renal fibrosis in DKD patients with favorable safety profile in clinical use.
	Total Glucosides of Paeony (TGP)	Inhibits JAK2/STAT3 pathway, suppresses macrophage activation, reduces renal inflammation and fibrosis.	Preclinical studies in Wistar rats with STZ-induced DKD.	Inhibited macrophage infiltration and fibrosis, reduced progression of DKD.	No clinical data yet for DKD.		Potential anti-inflammatory and fibrosis-reducing effects make it promising for DKD management.
	Paeoniflorin	Inhibits JAK2/STAT3 pathway, reduces macrophage infiltration and inflammatory responses.	Preclinical studies in STZ-induced C57BL/6J mice.	Alleviated kidney inflammation and fibrosis, improved kidney protection.	No significant adverse reactions in clinical trials.		May provide effective anti-inflammatory and protective effects against DKD.
	Isoliquiritigenin	Inhibits JAK2/STAT3 pathway, reduces inflammation and oxidative stress, protects against renal fibrosis.	Preclinical studies in HFD/STZ-induced SD rats.	Reduced renal fibrosis and inflammation, decreased IL-6 and ICAM-1 levels.	Minimal side effects reported.		Promising in alleviating oxidative stress and fibrosis, potential for DKD prevention.
	Momordica Charantia	Inhibits JAK2/STAT3/STAT5/SOCS3/4 pathways, reduces renal inflammation and fibrosis.	Preclinical studies in STZ-induced Wistar rats.	Reduced renal inflammatory response, modulated JAK/STAT pathways, reduced kidney damage.	No major adverse effects, but further studies on long-term use are needed.		Potential for modulating inflammatory pathways, a promising candidate for DKD prevention.
	Danzhi Jiangtang Capsule	Inhibits JAK/STAT pathway, reduces oxidative stress and inflammation in DKD.	Preclinical studies in HFD/STZ-induced SD rats and AGE-induced GMC model.	Reduced renal dysfunction, alleviated inflammatory injury in rats, associated with JAK/STAT inhibition.	Limited clinical data, but *in vitro* and animal studies suggest efficacy.		Potential as a complementary treatment for DKD by targeting oxidative stress and inflammation.
	ErHuang Formula	Inhibits CXCL6/JAK/STAT3 pathway, reduces inflammation fibrosis, and improves kidney function.	Preclinical studies in HFD/STZ-induced SD rats and HG-induced NRK-49F cells.	Reduced fibrosis, decreased inflammation and renal dysfunction.	Need for more extensive clinical trials.		Potential to reduce renal fibrosis and inflammation, useful in DKD management.
Adhesion and chemokine molecule inhibitors	*ASP8232* (VAP-1 inhibitor), *Emapticap Pegol* (CCL2-CCR2 inhibitor), *NOX-A12* (CXCL12 inhibitor)	Blockade of adhesion molecules and chemokines, reducing immune cell migration and kidney inflammation	Clinical (Phase II), Preclinical	Reduced proteinuria, renal protection, slowed progression of kidney injury	Limited options for targeting adhesion molecules need for additional clinical research	[155-161,162]	Targeting adhesion molecules can block immune cell migration to the kidneys, reducing inflammation and fibrosis in DKD.

JAK-STAT inhibitors

JAK inhibitors, such as *tofacitinib* (JAK1/3) and *baricitinib* (JAK1/2), have shown effectiveness in treating inflammatory and autoimmune diseases, including rheumatoid arthritis [143]. *Ruxolitinib*, another JAK1/2 inhibitor, is approved for myelofibrosis [144] and has also been studied in autoimmune diseases like Crohn's disease and psoriasis [145, 146]. In early clinical trials, JAK inhibitors have demonstrated potential in treating DKD by improving renal function and reducing inflammatory markers [147, 148]. *Baricitinib*, for instance, has reduced albuminuria and inflammation in type 2 diabetic patients with DKD (NCT01683409). However, the long-term safety of these treatments, especially concerning anemia and infection risks, requires further investigation. Additionally, *Ruxolitinib* and *Nifuroxazide*, which inhibit the JAK/STAT pathway, have shown promise in experimental models for DKD treatment by reducing fibrosis and inflammation [149, 150]. Natural products like *Sinomenine*, *Silymarin* and *Paeoniflorin* have also been studied for their ability to modulate the JAK/STAT pathway and offer potential therapeutic benefits for DKD [151, 152]. Other medications, such as liraglutide and vitamin D, have been found to inhibit the JAK/STAT pathway and alleviate DKD-related inflammation and fibrosis, although further clinical trials are needed to confirm their long-term efficacy and safety [153, 154].

Adhesion and chemokine molecule inhibition in DKD

Adhesion molecules (ICAM-1, VCAM-1, VAP-1) and chemokines (e. g., CCL2) contribute to kidney inflammation and damage in DKD. Targeting adhesion molecules with VAP-1 inhibitors like *ASP8232* and blocking the CCL2-CCR2 pathway with *Emapticap Pegol* reduced proteinuria in Phase II trials [155-161]. CXCL12 inhibition also alleviated kidney damage in diabetic mice [162].

Critical analysis

The development of experimental drugs for DKD has been notably slow despite promising preclinical results and the urgent need for effective therapies. One significant reason for this lag is the high attrition rate during clinical trials, often due to issues related to safety, efficacy and side effects. Many drugs that show potential in animal models fail to replicate these outcomes in human trials. For example, while antioxidants like ALA and curcumin show positive effects in preclinical studies, they often have limited bioavailability or cause mild side effects in humans which hampers their clinical adoption. Similarly, AGE formation inhibitors like *Aminoguanidine*, despite showing promise in animal models, were discontinued in human trials due to toxicity concerns. Additionally, the complexity of DKD's pathophysiology, involving multiple pathways such as OS, inflammation, fibrosis and metabolic dysregulation, makes it difficult to pinpoint a single therapeutic target. As a result, clinical trials frequently fail to achieve the desired outcomes, slowing the development of effective treatments.

Moreover, regulatory and financial hurdles further delay the introduction of new DKD therapies. Clinical trials, particularly those for chronic conditions like DKD, require long follow-up periods to assess long-term safety and effectiveness, which increases both time and cost. This is particularly challenging for drugs targeting multiple pathways, such as mTOR inhibitors or ETA, where potential side effects like fluid retention or cardiovascular risks must be carefully managed. Limited funding, especially for phase III trials and a lack of consensus on optimal biomarkers for disease progression, also contribute to the slow pace of drug development. As a result, while the number of experimental drugs in the DKD pipeline is growing, many faces significant obstacles before they can be approved for widespread clinical use, further delaying advances in treatment for this progressive and debilitating disease.

Table 3: Comparison of current drugs Vs experimental drugs to prevent DKD

Criteria	Current treatment options	Experimental treatment options
Therapeutic efficacy	-DPP-4 Inhibitors: Improve insulin secretion and reduce albuminuria. Proven efficacy in DKD management. -SGLT2 Inhibitors: Reduce glucose reabsorption and albuminuria, slow progression of kidney disease. -ACE Inhibitors/ARBs: Reduce proteinuria, control BP and protect kidney function.	-Antioxidants (*ALA, Resveratrol, Curcumin, Sulbutiamine, Schisandrin B*): Show promising effects on reducing OS, improving kidney function and preventing fibrosis in preclinical and early clinical trials. -AGE Formation Inhibitors (*DPHC, Aminoguanidine*): Show potential in reducing kidney damage by preventing AGE-RAGE interaction. -ARI: Potential to reduce kidney damage by inhibiting the polyol pathway. -MRA (*Esaxerenone*): Show efficacy in reducing albuminuria independent of BP. -Endothelin-1 Receptor Antagonist (*Ambrisentan, Macitentan, Bosentan*): Potential to reduce glomerular permeability and inflammation. -mTOR Inhibitors (*Rapamycin, Tripterygium Glycoside*): Demonstrate efficacy in reducing kidney injury, improving glomerular function and decreasing inflammation and fibrosis. -TNF-α Inhibitors (*Infliximab, Etanercept*): Show potential in reducing kidney inflammation and albuminuria. -*PTX*: Demonstrates potential in improving kidney function and reducing inflammation. -Nox1/4 Inhibitors (*GKT137831, NOX-E36*): Show potential to reduce ROS production and kidney damage. -Nrf2 Activators (*Bardoxolone Methyl*): Demonstrated increased glomerular filtration rate, though concerns over cardiovascular safety exist. -JAK-STAT Inhibitors (*Baricitinib*): Reduced proteinuria in early-phase trials, suggesting efficacy in DKD management. -Adhesion and Chemokine Molecule Inhibitors: Target adhesion molecules to reduce inflammation and kidney damage.
Cost	-Moderate to High: SGLT2 inhibitors, GLP-1 agonists, and other medications like ACE inhibitors or ARBs can be expensive, especially newer drugs like SGLT2 inhibitors.	-Varies: Many experimental treatments are still in clinical trials and are not yet commercially available, making the cost difficult to determine. Some therapies might be cost-effective if they enter the market but others, especially novel biologics or small molecules, may be expensive.

CONCLUSION

In conclusion, while significant progress has been made in identifying and implementing strategies to prevent DKD, many of the current interventions primarily focus on slowing disease progression rather than offering definitive prevention. Lifestyle modifications such as weight loss, physical activity and dietary changes remain foundational in reducing the risk of DKD and pharmacological treatments such as ACE inhibitors, ARB and SGLT2 inhibitors have demonstrated efficacy in mitigating the onset of kidney complications. However, these interventions are not without limitations and while they can delay the progression of kidney damage, they do not fully prevent the disease in all patients.

Given the promising yet early-stage nature of many emerging therapies such as antioxidants (e. g., *ALA, Resveratrol, Curcumin*), MRA and novel agents like JAK-STAT inhibitors, the urgency for more extensive and rigorous clinical trials becomes evident. Early clinical data may suggest potential benefits, but they are not sufficient to justify the optimistic outlook that some of these therapies might prevent DKD in the long term. Therefore, a key priority is the acceleration of clinical studies to validate these promising treatments, particularly for high-risk populations who may benefit most from early intervention.

Additionally, as DKD is a complex and multifactorial disease, a more personalized approach to prevention by incorporating individual risk factors such as age, comorbid conditions and underlying cardiovascular risk will be essential in optimizing prevention strategies. Tailoring interventions to the specific needs of each patient has the potential to prevent the onset of DKD while minimizing adverse effects. Ultimately, a concerted effort to advance clinical trials and refine prevention strategies will be crucial in reducing the burden of DKD and improving outcomes for those at risk.

ACKNOWLEDGEMENT

In writing this review article, I wish to express my sincere appreciation to everyone who supported and contributed to its development. I am especially grateful to my colleagues and mentors, whose insightful feedback and constructive critiques were instrumental in guiding this work. I also want to acknowledge the researchers whose groundbreaking studies laid the groundwork for this systematic review; their dedication and innovative approaches have greatly enhanced this field.

FUNDING

No financial support, grants, or other assistance was provided.

AUTHORS CONTRIBUTIONS

All authors played a role in the conception and design of the study. B. Dharani, S. Nazrin, and Stephy Sebastian handled data collection and analysis. The initial draft of the manuscript was prepared by B. Dharani and S. Nazrin, while Suba A. assisted in gathering articles. Each author reviewed earlier drafts, provided feedback, and approved the final version.

CONFLICTS OF INTERESTS

The authors declare that there is no conflict of interest.

REFERENCES

1. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. Lancet. 2016;387(10027):1513-30. doi: 10.1016/S0140-6736(16)00618-8, PMID 27061677.
2. Federation ID. IDF diabetes atlas brussels. Belgium: international diabetes federation; 2021.
3. Garg AX, Kiberd BA, Clark WF, Haynes RB, Clase CM. Albuminuria and renal insufficiency prevalence guides population screening: results from the NHANES III. Kidney Int. 2002;61(6):2165-75. doi: 10.1046/j.1523-1755.2002.00356.x, PMID 12028457.
4. Naaman SC, Bakris GL. Diabetic nephropathy: update on pillars of therapy slowing progression. Diabetes Care. 2023;46(9):1574-86. doi: 10.2337/dci23-0030, PMID 37625003.
5. Sagoo MK, Gnudi L. Diabetic nephropathy: an overview. Methods Mol Biol. 2020;2067:3-7. doi: 10.1007/978-1-4939-9841-8_1, PMID 31701441.
6. Thomas MC, Brownlee M, Susztak K, Sharma K, Jandeleit Dahm KA, Zoungas S. Diabetic kidney disease. Nat Rev Dis Primers. 2015 Jul 30;1:15018. doi: 10.1038/nrdp.2015.18, PMID 27188921.
7. Papadopoulou Marketou N, Kanaka Gantenbein C, Marketos N, Chrousos GP, Papassotiriou I. Biomarkers of diabetic nephropathy: a 2017 update. Crit Rev Clin Lab Sci. 2017;54(5):326-42. doi: 10.1080/10408363.2017.1377682, PMID 28956668.
8. Carey RM, Wang ZQ, Siragy HM. Role of the angiotensin type 2 receptor in the regulation of blood pressure and renal function. Hypertension. 2000;35(1 Pt 2):155-63. doi: 10.1161/01.hyp.35.1.155, PMID 10642292.
9. Ames MK, Atkins CE, Pitt B. The rennin angiotensin aldosterone system and its suppression. J Vet Intern Med. 2019;33(2):363-82. doi: 10.1111/jvim.15454, PMID 30806496.
10. Ruiz Ortega M, Lorenzo O, Suzuki Y, Ruperez M, Egido J. Proinflammatory actions of angiotensins. Curr Opin Nephrol Hypertens. 2001;10(3):321-9. doi: 10.1097/00041552-200105000-00005, PMID 11342793.
11. Poursharif S, Hamza S, Braam B. Changes in proximal tubular reabsorption modulate microvascular regulation via the TGF system. Int J Mol Sci. 2022;23(19)11203. doi: 10.3390/ijms231911203.
12. Tuttle KR. Back to the future: glomerular hyperfiltration and the diabetic kidney. Diabetes. 2017;66(1):14-6. doi: 10.2337/dbi16-0056, PMID 27999101.
13. Heerspink HJ, Perkins BA, Fitchett DH, Husain M, Cherney DZ. Sodium-glucose cotransporter 2 inhibitors in the treatment of diabetes mellitus: cardiovascular and kidney effects potential mechanisms and clinical applications. Circulation. 2016;134(10):752-72. doi: 10.1161/circulationaha.116.021887, PMID 27470878.
14. Tonneijck L, Muskiet MH, Smits MM, Van Bommel EJ, Heerspink HJ, Van Raalte DH. Glomerular hyperfiltration in diabetes: mechanisms clinical significance and treatment. J Am Soc Nephrol. 2017;28(4):1023-39. doi: 10.1681/ASN.2016060666, PMID 28143897.
15. Astor BC, Hallan SI, Miller ER 3rd, Yeung E, Coresh J. Glomerular filtration rate albuminuria and risk of cardiovascular and all-cause mortality in the US population. Am J Epidemiol. 2008;167(10):1226-34. doi: 10.1093/aje/kwn033, PMID 18385206.
16. Bello AK, Hemmelgarn B, Lloyd A, James MT, Manns BJ, Klarenbach S. Associations among estimated glomerular filtration rate proteinuria and adverse cardiovascular outcomes. Clin J Am Soc Nephrol. 2011;6(6):1418-26. doi: 10.2215/CJN.09741110, PMID 21527648.
17. El Sayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D. Chronic kidney disease and risk management: standards of care in diabetes-2023. Diabetes Care. 2023;46 Suppl 1:S191-202. doi: 10.2337/dc23-S011, PMID 36507634.
18. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on kidney in cardiovascular disease high blood pressure research clinical cardiology and epidemiology and prevention. Circulation. 2003;108(17):2154-69. doi: 10.1161/01.CIR.0000095676.90936.80, PMID 14581387.
19. Cantero Navarro E, Rayego Mateos S, Orejudo M, Tejedor Santamaria L, Tejera Munoz A, Sanz AB. Role of macrophages and related cytokines in kidney disease. Front Med (Lausanne). 2021 Jul 8;8:688060. doi: 10.3389/fmed.2021.688060, PMID 34307414.
20. Tesch GH. Macrophages and diabetic nephropathy. Semin Nephrol. 2010;30(3):290-301. doi: 10.1016/j.semnephrol.2010.03.007, PMID 20620673.
21. Usher MG, Duan SZ, Ivaschenko CY, Frieler RA, Berger S, Schutz G. Myeloid mineralocorticoid receptor controls macrophage polarization and cardiovascular hypertrophy and remodeling in mice. J Clin Invest. 2010;120(9):3350-64. doi: 10.1172/JCI41080, PMID 20697155.
22. American Diabetes Association. 6. Glycemic targets: standards of Medical Care in diabetes-2018. Diabetes Care. 2018 Jan;41 Suppl 1:S55-64. doi: 10.2337/dc18-S006, PMID 29222377.
23. Qaseem A, Wilt TJ, Kansagara D, Horwitch C, Barry MJ, Forciea MA. Hemoglobin A1c targets for glycemic control with pharmacologic therapy for nonpregnant adults with type 2 diabetes mellitus: a guidance statement update from the American College of Physicians. Ann Intern Med. 2018;168(8):569-76. doi: 10.7326/M17-0939, PMID 29507945.
24. Groop PH, Cooper ME, Perkovic V, Emser A, Woerle HJ, Von Eynatten M. Linagliptin lowers albuminuria on top of recommended standard treatment in patients with type 2 diabetes and renal dysfunction. Diabetes Care. 2013;36(11):3460-8. doi: 10.2337/dc13-0323, PMID 24026560.
25. Groop PH, Cooper ME, Perkovic V, Hocher B, Kanasaki K, Haneda M. Linagliptin and its effects on hyperglycaemia and albuminuria in patients with type 2 diabetes and renal dysfunction: the randomized MARLINA-T2D trial. Diabetes Obes Metab. 2017;19(11):1610-9. doi: 10.1111/dom.13041, PMID 28636754.
26. Scirica BM, Braunwald E, SAVOR-TIMI RI. 53 steering committee and investigators. Heart failure saxagliptin and diabetes mellitus: observations from the SAVOR-TIMI 53 randomized trial. Circulation. 2014;132(15):1579-88.
27. Marso SP, Daniels GH, Brown Frandsen K, Kristensen P, Mann JF, Nauck MA. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2016;375(4):311-22. doi: 10.1056/NEJMoa1603827, PMID 27295427.
28. Fujita H, Morii T, Fujishima H, Sato T, Shimizu T, Hosoba M. The protective roles of GLP-1R signaling in diabetic nephropathy: possible mechanism and therapeutic potential. Kidney Int. 2014;85(3):579-89. doi: 10.1038/ki.2013.427, PMID 24152968.

29. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jodar E, Leiter LA. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2016;375(19):1834-44. doi: 10.1056/NEJMoa1607141, PMID 27633186.
30. Wanner C, Inzucchi SE, Lachin JM, Fitchett D, Von Eynatten M, Mattheus M. Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med. 2016;375(4):323-34. doi: 10.1056/NEJMoa1515920, PMID 27299675.
31. Barnett AH, Mithal A, Manassie J, Jones R, Rattunde H, Woerle HJ. Efficacy and safety of empagliflozin added to existing antidiabetes treatment in patients with type-2 diabetes and chronic kidney disease: a randomised double blind placebo controlled trial. Lancet Diabetes Endocrinol. 2014;2(5):369-84. doi: 10.1016/S2213-8587(13)70208-0, PMID 24795251.
32. Sarafidis PA, Bakris GL. Protection of the kidney by thiazolidinediones: an assessment from bench to bedside. Kidney Int. 2006;70(7):1223-33. doi: 10.1038/sj.ki.5001620, PMID 16883325.
33. Whelton PK, Carey RM, Aronow WS. PCNA guideline for the prevention detection evaluation and management of high blood pressure in adults: a report of the American college of cardiology/American heart association task force on clinical practice guidelines. J Am Coll Cardiol. 2017;71(19):e127-248. doi: 10.1016/j.jacc.2017.11.005, PMID 29146533.
34. ACCORD Study Group, Cushman WC, Evans GW, Byington RP, Goff DC JR, Grimm RH JR. Effects of intensive blood pressure control in type 2 diabetes mellitus. N Engl J Med. 2010;362(17):1575-85. doi: 10.1056/NEJMoa1001286, PMID 20228401.
35. LV J, Perkovic V, Foote CV, Craig ME, Craig JC, Strippoli GF. Antihypertensive agents for preventing diabetic kidney disease. Cochrane Database Syst Rev. 2012;12(12):CD004136. doi: 10.1002/14651858.CD004136.pub3, PMID 23235603.
36. Haller H, Ito S, Izzo JL, Januszewicz A, Katayama S, Menne J. Olmesartan for the delay or prevention of microalbuminuria in type 2 diabetes. N Engl J Med. 2011;364(10):907-17. doi: 10.1056/NEJMoa1007994, PMID 21388309.
37. Currie G, Taylor AH, Fujita T, Ohtsu H, Lindhardt M, Rossing P. Effect of mineralocorticoid receptor antagonists on proteinuria and progression of chronic kidney disease: a systematic review and meta-analysis. BMC Nephrol. 2016;17(1):127. doi: 10.1186/s12882-016-0337-0, PMID 27609359.
38. Bolignano D, Palmer SC, Navaneethan SD, Strippoli GF. Aldosterone antagonists for preventing the progression of chronic kidney disease. Cochrane Database Syst Rev. 2014;(4):CD007004. doi: 10.1002/14651858.CD007004.pub3, PMID 24782282.
39. Menne J, Ritz E, Ruilope LM, Chatzikyrkou C, Viberti G, Haller H. The randomized olmesartan and diabetes microalbuminuria prevention (roadmap) observational follow up study: benefits of ras blockade with *olmesartan* treatment are sustained after study discontinuation. J Am Heart Assoc. 2014;3(2):e000810. doi: 10.1161/jaha.114.000810, PMID 24772521.
40. Berbenetz NM, Mrkobrada M. Mineralocorticoid receptor antagonists for heart failure: systematic review and meta-analysis. BMC Cardiovasc Disord. 2016;16(1):246. doi: 10.1186/s12872-016-0425-x, PMID 27905877.
41. Abdelhakim AM, Abd El Gawad M. Impact of mineralocorticoid receptor antagonist in renal transplant patients: a systematic review and meta-analysis of randomized controlled trials. J Nephrol. 2020;33(3):529-38. doi: 10.1007/s40620-019-00681-4, PMID 31828668.
42. Tromp J, Ouwerkerk W, Van Veldhuisen DJ, Hillege HL, Richards AM, Van Der Meer P. A systematic review and network metaanalysis of pharmacological treatment of heart failure with reduced ejection fraction. JACC Heart Fail. 2020;33(3):73-84.
43. Chung EY, Ruospo M, Natale P, Bolignano D, Navaneethan SD, Palmer SC. Aldosterone antagonists in addition to renin angiotensin system antagonists for preventing the progression of chronic kidney disease. Cochrane Database Syst Rev. 2020;10(10):CD007004. doi: 10.1002/14651858.CD007004.pub4, PMID 33107592.
44. Rossing K, Schjoedt KJ, Smidt UM, Boomsma F, Parving HH. Beneficial effects of adding spironolactone to recommended antihypertensive treatment in diabetic nephropathy: a randomized double masked cross over study. Diabetes Care. 2005;28(9):2106-12. doi: 10.2337/diacare.28.9.2106, PMID 16123474.
45. Esteghamati A, Noshad S, Jarrah S, Mousavizadeh M, Khoee SH, Nakhjavani M. Long term effects of addition of mineralocorticoid receptor antagonist to angiotensin II receptor blocker in patients with diabetic nephropathy: a randomized clinical trial. Nephrol Dial Transplant. 2013;28(11):2823-33. doi: 10.1093/ndt/gft281, PMID 24009294.
46. Epstein M, Williams GH, Weinberger M, Lewin A, Krause S, Mukherjee R. Selective aldosterone blockade with eplerenone reduces albuminuria in patients with type 2 diabetes. Clin J Am Soc Nephrol. 2006;1(5):940-51. doi: 10.2215/CJN.00240106, PMID 17699311.
47. El Mokadem M, Abd El Hady Y, Aziz A. A prospective single blind randomized trial of ramipril eplerenone and their combination in type 2 diabetic nephropathy. Cardiorenal Med. 2020;10(6):392-401. doi: 10.1159/000508670, PMID 32998143.
48. Bertocchio JP, Barbe C, Lavaud S, Toupance O, Nazeyrollas P, Jaisser F. Safety of eplerenone for kidney transplant recipients with impaired renal function and receiving cyclosporine A. Plos One. 2016;11(4):e0153635. doi: 10.1371/journal.pone.0153635, PMID 27088859.
49. Bakris GL, Agarwal R, Chan JC, Cooper ME, Gansevoort RT, Haller H. Effect of finerenone on albuminuria in patients with diabetic nephropathy: a randomized clinical trial. JAMA. 2015;314(9):884-94. doi: 10.1001/jama.2015.10081, PMID 26325557.
50. Bakris GL, Agarwal R, Anker SD, Pitt B, Ruilope LM, Rossing P. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. N Engl J Med. 2020;383(23):2219-29. doi: 10.1056/NEJMoa2025845, PMID 33264825.
51. Ito S, Shikata K, Nangaku M, Okuda Y, Sawanobori T. Efficacy and safety of esaxerenone (CS− 3150) for the treatment of type-2 diabetes with microalbuminuria: a randomized double blind placebo controlled phase II trial. Clin J Am Soc Nephrol. 2019;14(8):1161-72. doi: 10.2215/CJN.14751218, PMID 31248950.
52. Ito S, Kashihara N, Shikata K, Nangaku M, Wada T, Okuda Y. Esaxerenone (CS-3150) in patients with type 2 diabetes and microalbuminuria (esax-dn): phase 3 randomized controlled clinical trial. Clin J Am Soc Nephrol. 2020;15(12):1715-27. doi: 10.2215/CJN.06870520, PMID 33239409.
53. Bakris G, Pergola PE, Delgado B, Genov D, Doliashvili T, VO N. Effect of KBP-5074 on blood pressure in advanced chronic kidney disease: results of the block CKD study. Hypertension. 2021;78(1):74-81. doi: 10.1161/hypertensionaha.121.17073, PMID 33966452.
54. Grdovic N, Rajic J, Arambasic Jovanovic J, Dinic S, Tolic A, Dordevic M. α-Lipoic acid increases collagen synthesis and deposition in nondiabetic and diabetic rat kidneys. Oxid Med Cell Longev. 2021;2021:6669352. doi: 10.1155/2021/6669352, PMID 33777319.
55. Charlton A, Garzarella J, Jandeleit Dahm KA, Jha JC. Oxidative stress and inflammation in renal and cardiovascular complications of diabetes. Biology (Basel). 2020;10(1):18. doi: 10.3390/biology10010018, PMID 33396868.
56. Zhang H, MU J, DU J, Feng Y, XU W, Bai M. *Alpha lipoic acid* could attenuate the effect of chemerin induced diabetic nephropathy progression. Iran J Basic Med Sci. 2021;24(8):1107-16. doi: 10.22038/ijbms.2021.50792.11570, PMID 34804428.
57. Vakali E, Rigopoulos D, Carrillo AE, Flouris AD, Dinas PC. Effects of *alpha* lipoic acid supplementation on human diabetic nephropathy: a systematic review and meta-analysis. Curr Diabetes Rev. 2022;18(6):e140921196457. doi: 10.2174/1573399817666210914103329, PMID 34521329.
58. Jiang M, Sun H, Zhang H, Cheng Y, Zhai C. ALA/*LA* inhibited renal tubulointerstitial fibrosis of DKD db/db mice induced by oxidative stress. Research square; 2024. doi: 10.21203/rs.3.rs-3956527/v1.
59. Jeffrey S, Samraj PI, Raj BS. The role of *alpha lipoic acid* supplementation in the prevention of diabetes complications: a comprehensive review of clinical trials. Curr Diabetes Rev. 2021;17(9):e011821190404. doi: 10.2174/1573399817666210118145550, PMID 33461470.

60. Gowd V, Kang Q, Wang Q, Wang Q, Chen F, Cheng KW. Resveratrol: evidence for its nephroprotective effect in diabetic nephropathy. Adv Nutr. 2020;11(6):1555-68. doi: 10.1093/advances/nmaa075, PMID 32577714.
61. Xian Y, Gao Y, LV W, MA X, HU J, Chi J. Resveratrol prevents diabetic nephropathy by reducing chronic inflammation and improving the blood glucose memory effect in non obese diabetic mice. Naunyn Schmiedebergs Arch Pharmacol. 2020;393(10):2009-17. doi: 10.1007/s00210-019-01777-1, PMID 31970441.
62. Salami M, Salami R, Mafi A, Aarabi MH, Vakili O, Asemi Z. Therapeutic potential of resveratrol in diabetic nephropathy according to molecular signaling. Curr Mol Pharmacol. 2022;15(5):716-35. doi: 10.2174/1874467215666211217122523, PMID 34923951.
63. LI KX, JI MJ, Sun HJ. An updated pharmacological insight of resveratrol in the treatment of diabetic nephropathy. Gene. 2021;780:145532. doi: 10.1016/j.gene.2021.145532, PMID 33631244.
64. Sattarinezhad A, Roozbeh J, Shirazi Yeganeh B, Omrani GR, Shams M. Resveratrol reduces albuminuria in diabetic nephropathy: a randomized double-blind placebo-controlled clinical trial. Diabetes Metab. 2019;45(1):53-9. doi: 10.1016/j.diabet.2018.05.010, PMID 29983230.
65. Chen S, LI B, Chen L, Jiang H. Uncovering the mechanism of resveratrol in the treatment of diabetic kidney disease based on network pharmacology molecular docking and experimental validation. J Transl Med. 2023;21(1):380. doi: 10.1186/s12967-023-04233-0, PMID 37308949.
66. Zhu X, XU X, DU C, SU Y, Yin L, Tan X. An examination of the protective effects and molecular mechanisms of curcumin a polyphenol curcuminoid in diabetic nephropathy. Biomed Pharmacother. 2022;153:113438. doi: 10.1016/j.biopha.2022.113438, PMID 36076553.
67. Pricci M, Girardi B, Giorgio F, Losurdo G, Ierardi E, DI Leo A. Curcumin and colorectal cancer: from basic to clinical evidences. Int J Mol Sci. 2020;21(7):2364. doi: 10.3390/ijms21072364, PMID 32235371.
68. Asadi S, Goodarzi MT, Karimi J, Hashemnia M, Khodadadi I. Does curcumin or metformin attenuate oxidative stress and diabetic nephropathy in rats? J Nephropathol. 2018;8(1):8. doi: 10.15171/jnp.2019.08.
69. Al Tamimi JZ, Al Farga NA, Alshammari AM, Mowyna B, Yahya MN. Curcumin reverses diabetic nephropathy in streptozotocin-induced diabetes in rats by inhibition of PKC/p66Shc axis and activation of FOXO-3a. J Nutr Biochem. 2021 Jan;87:108515. doi: 10.1016/j.jnutbio.2020.108515.
70. Gao L, LV Q, Wang Y, Zhang D, Ding W, Cao L. Research on mechanism of curcumin with chitosan nanoparticles in regulating the activity of podocytes in diabetic nephropathy through alleviating oxidative stress and inflammation. Sci Adv Mater. 2022;14(4):752-9. doi: 10.1166/sam.2022.4249.
71. Ganugula R, Nuthalapati NK, Dwivedi S, Zou D, Arora M, Friend R. Nanocurcumin combined with insulin alleviates diabetic kidney disease through P38/P53 signaling axis. J Control Release. 2023;353:621-33. doi: 10.1016/j.jconrel.2022.12.012, PMID 36503070.
72. Shing CM, Adams MJ, Fassett RG, Coombes JS. Nutritional compounds influence tissue factor expression and inflammation of chronic kidney disease patients *in vitro*. Nutrition. 2011;27(9):967-72. doi: 10.1016/j.nut.2010.10.014, PMID 21295946.
73. Alvarenga L, Salarolli R, Cardozo LF, Santos RS, DE Brito JS, Kemp JA. Impact of curcumin supplementation on expression of inflammatory transcription factors in hemodialysis patients: a pilot randomized double-blind controlled study. Clin Nutr. 2020;39(12):3594-600. doi: 10.1016/j.clnu.2020.03.007, PMID 32204978.
74. Alvarenga L, Cardozo LF, DA Cruz BO, Paiva BR, Fouque D, Mafra D. Curcumin supplementation improves oxidative stress and inflammation biomarkers in patients undergoing hemodialysis: a secondary analysis of a randomized controlled trial. Int Urol Nephrol. 2022;54(10):2645-52. doi: 10.1007/s11255-022-03182-9, PMID 35347555.
75. Salarolli RT, Alvarenga L, Cardozo LF, Teixeira KT, DE SG Moreira L, Lima JD. Can curcumin supplementation reduce plasma levels of gut-derived uremic toxins in hemodialysis patients? A pilot randomized double-blind controlled study. Int Urol Nephrol. 2021;53(6):1231-8. doi: 10.1007/s11255-020-02760-z, PMID 33438085.
76. Ghaiad HR, Ali SO, Al Mokaddem AK, Abdelmonem M. Regulation of PKC/TLR-4/NF-kB signaling by sulbutiamine improves diabetic nephropathy in rats. Chem Biol Interact. 2023 Aug 25;381:110544. doi: 10.1016/j.cbi.2023.110544, PMID 37224990.
77. Liu W, LI F, Guo D, DU C, Zhao S, LI J. Schisandrin B alleviates renal tubular cell epithelial-mesenchymal transition and mitochondrial dysfunction by kielin/chordin-like protein upregulation via akt pathway inactivation and adenosine 5 monophosphate (amp) activated protein kinase pathway activation in diabetic kidney disease. Molecules. 2023 Nov 29;28(23):7851. doi: 10.3390/molecules28237851, PMID 38067580.
78. Cho CH, Yoo G, Kim M, Lee CJ, Choi IW, Ryu B. Diphlorethohydroxycarmalol a phlorotannin contained in brown edible seaweed Ishige okamurae, prevents AGE-related diabetic nephropathy by suppression of AGE-RAGE interaction. Food Biosci. 2023 Jun;53:102659. doi: 10.1016/j.fbio.2023.102659.
79. Coughlan MT, Cooper ME, Forbes JM. Can advanced glycation end-product inhibitors modulate more than one pathway to enhance renoprotection in diabetes? Ann N Y Acad Sci. 2005;1043(1):750-8. doi: 10.1196/annals.1333.087, PMID 16037302.
80. Bolton WK, Cattran DC, Williams ME, Adler SG, Appel GB, Cartwright K. Randomized trial of an inhibitor of formation of advanced glycation end products in diabetic nephropathy. Am J Nephrol. 2004;24(1):32-40. doi: 10.1159/000075627, PMID 14685005.
81. Forbes JM, Thorpe SR, Thallas Bonke V, Pete J, Thomas MC, Deemer ER. Modulation of soluble receptor for advanced glycation end products by angiotensin-converting enzyme-1 inhibition in diabetic nephropathy. J Am Soc Nephrol. 2005;16(8):2363-72. doi: 10.1681/ASN.2005010062, PMID 15930093.
82. Yang L, XU L, Hao X, Song Z, Zhang X, Liu P. An aldose reductase inhibitor WJ-*39* ameliorates renal tubular injury in diabetic nephropathy by activating PINK1/Parkin signaling. Eur J Pharmacol. 2024;967:176376. doi: 10.1016/j.ejphar.2024.176376, PMID 38336014.
83. Song T, Wang R, Zhou X, Chen W, Chen Y, Liu Z. Metabolomics and molecular dynamics unveil the therapeutic potential of epalrestat in diabetic nephropathy. Int Immunopharmacol. 2024;140:112812. doi: 10.1016/j.intimp.2024.112812, PMID 39094360.
84. Okuda Y, Ito S, Kashihara N, Shikata K, Nangaku M, Wada T. The renoprotective effect of esaxerenone independent of blood pressure lowering: a post hoc mediation analysis of the ESAX-DN trial. Hypertens Res. 2023;46(2):437-44. doi: 10.1038/s41440-022-01008-w, PMID 36100672.
85. Liang F, Glascock CB, Schafer DL, Sandoval J, Cable LA, Melvin L. Darusentan is a potent inhibitor of endothelin signaling and function in both large and small arteries. Can J Physiol Pharmacol. 2010;88(8):840-9. doi: 10.1139/Y10-061, PMID 20725142.
86. Heerspink HJ, Parving HH, Andress DL, Bakris G, Correa Rotter R, Hou FF. Atrasentan and renal events in patients with type 2 diabetes and chronic kidney disease (SONAR): a double-blind, randomised placebo-controlled trial. Lancet. 2019;393(10184):1937-47. doi: 10.1016/S0140-6736(19)30772-X, PMID 30995972.
87. Scott LJ. Sitaxentan: in pulmonary arterial hypertension. Drugs. 2007;67(5):761-70. doi: 10.2165/00003495-200767050-00007, PMID 17385944.
88. Enseleit F, Luscher TF, Ruschitzka F. Darusentan a selective endothelin a receptor antagonist for the oral treatment of resistant hypertension. Ther Adv Cardiovasc Dis. 2010;4(4):231-40. doi: 10.1177/1753944710373785, PMID 20660536.

89. Mann JF, Green D, Jamerson K, Ruilope LM, Kuranoff SJ, Littke T. Avosentan for overt diabetic nephropathy. J Am Soc Nephrol. 2010;21(3):527-35. doi: 10.1681/ASN.2009060593, PMID 20167702.
90. Anguiano L, Riera M, Pascual J, Soler MJ. Endothelin blockade in diabetic kidney disease. J Clin Med. 2015;4(6):1171-92. doi: 10.3390/jcm4061171, PMID 26239552.
91. Zhou Y, Chi J, Huang Y, Dong B, LV W, Wang YG. Efficacy and safety of endothelin receptor antagonists in type 2 diabetic kidney disease: a systematic review and meta-analysis of randomized controlled trials. Diabet Med. 2021;38(1):e14411. doi: 10.1111/dme.14411, PMID 33000477.
92. Thomas MC. Targeting the pathobiology of diabetic kidney disease. Adv Chronic Kidney Dis. 2021;28(4):282-9. doi: 10.1053/j.ackd.2021.07.001, PMID 34922684.
93. Sharov AV, Burkhanova TM, Taskın Tok T, Babashkina MG, Safin DA. Computational analysis of molnupiravir. Int J Mol Sci. 2022;23(21):13026. doi: 10.3390/ijms232113026, PMID 36362453.
94. Zang N, Cui C, Guo X, Song J, HU H, Yang M. Cgas-sting activation contributes to podocyte injury in diabetic kidney disease. Iscience. 2022;25(10):105145. doi: 10.1016/j.isci.2022.105145, PMID 36176590.
95. Yang Z, Liu F, QU H, Wang H, Xiao X, Deng H. 1, 25(OH)2D3 protects β cell against high glucose-induced apoptosis through mTOR suppressing. Mol Cell Endocrinol. 2015 Oct 15;414:111-9. doi: 10.1016/j.mce.2015.07.023, PMID 26213322.
96. Shi L, Xiao C, Zhang Y, Xia Y, Zha H, Zhu J. Vitamin D/vitamin D receptor/Atg16L1 axis maintains podocyte autophagy and survival in diabetic kidney disease. Ren Fail. 2022;44(1):694-705. doi: 10.1080/0886022X.2022.2063744, PMID 35469547.
97. Chen DP, MA YP, Zhuo L, Zhang Z, Zou GM, Yang Y. 1,25-dihydroxyvitamin D3 inhibits the proliferation of rat mesangial cells induced by high glucose via DDIT4. Oncotarget. 2018;9(1):418-27. doi: 10.18632/oncotarget.23063, PMID 29416624.
98. Wang B, Peng L, Ouyang H, Wang L, HE D, Zhong J. Induction of DDIT4 impairs autophagy through oxidative stress in dry eye. Invest Ophthalmol Vis Sci. 2019;60(8):2836-47. doi: 10.1167/iovs.19-27072, PMID 31266058.
99. Tervaert TW, Mooyaart AL, Amann K, Cohen AH, Cook HT, Drachenberg CB. Pathologic classification of diabetic nephropathy. J Am Soc Nephrol. 2010;21(4):556-63. doi: 10.1681/ASN.2010010010, PMID 20167701.
100. Herb M, Schramm M. Functions of ROS in macrophages and antimicrobial immunity. Antioxidants (Basel). 2021;10(2):313. doi: 10.3390/antiox10020313, PMID 33669824.
101. Kogot Levin A, Hinden L, Riahi Y, Israeli T, Tirosh B, Cerasi E. Proximal tubule mTORC1 is a central player in the pathophysiology of diabetic nephropathy and its correction by SGLT2 inhibitors. Cell Rep. 2020;32(4):107954. doi: 10.1016/j.celrep.2020.107954, PMID 32726619.
102. Reifsnyder PC, Flurkey K, TE A, Harrison DE. Rapamycin treatment benefits glucose metabolism in mouse models of type 2 diabetes. Aging (Albany NY). 2016;8(11):3120-30. doi: 10.18632/aging.101117, PMID 27922820.
103. Mori H, Inoki K, Masutani K, Wakabayashi Y, Komai K, Nakagawa R. The mTOR pathway is highly activated in diabetic nephropathy and rapamycin has a strong therapeutic potential. Biochem Biophys Res Commun. 2009;384(4):471-5. doi: 10.1016/j.bbrc.2009.04.136, PMID 19422788.
104. Murakami N, Riella LV, Funakoshi T. Risk of metabolic complications in kidney transplantation after conversion to mTOR inhibitor: a systematic review and meta-analysis. Am J Transplant. 2014;14(10):2317-27. doi: 10.1111/ajt.12852, PMID 25146383.
105. Paluri RK, Sonpavde G, Morgan C, Rojymon J, Mar AH, Gangaraju R. Renal toxicity with mammalian target of rapamycin inhibitors: a meta-analysis of randomized clinical trials. Oncol Rev. 2019;13(2):455. doi: 10.4081/oncol.2019.455, PMID 31857859.
106. Flaquer M, Lloberas N, Franquesa M, Torras J, Vidal A, Rosa JL. The combination of sirolimus and rosiglitazone produces a renoprotective effect on diabetic kidney disease in rats. Life Sci. 2010;87(5-6):147-53. doi: 10.1016/j.lfs.2010.06.004, PMID 20600147.
107. LI D, LU Z, XU Z, JI J, Zheng Z, Lin S. Spironolactone promotes autophagy via inhibiting PI3K/AKT/mTOR signalling pathway and reduce adhesive capacity damage in podocytes under mechanical stress. Biosci Rep. 2016;36(4):e00355. doi: 10.1042/BSR20160086, PMID 27129295.
108. Wang MZ, Wang J, Cao DW, TU Y, Liu BH, Yuan CC. Fucoidan alleviates renal fibrosis in diabetic kidney disease via inhibition of NLRP3 inflammasome-mediated podocyte pyroptosis. Front Pharmacol. 2022;13:790937. doi: 10.3389/fphar.2022.790937, PMID 35370636.
109. Liu H, Wang Q, Shi G, Yang W, Zhang Y, Chen W. Emodin ameliorates renal damage and podocyte injury in a rat model of diabetic nephropathy via regulating AMPK/Mtor mediated autophagy signaling pathway. Diabetes Metab Syndr Obes. 2021 Mar 18;14:1253-66. doi: 10.2147/DMSO.S299375, PMID 33776462.
110. LV L, Zhang J, Tian F, LI X, LI D, YU X. Arbutin protects HK-2 cells against high glucose-induced apoptosis and autophagy by up-regulating microRNA-27a. Artif Cells Nanomed Biotechnol. 2019;47(1):2940-7. doi: 10.1080/21691401.2019.1640231, PMID 31319730.
111. Wei L, Jian P, Erjiong H, Qihan Z. Ginkgetin alleviates high glucose evoked mesangial cell oxidative stress injury inflammation and extracellular matrix (ECM) deposition in an AMPK/mTOR mediated autophagy axis. Chem Biol Drug Des. 2021;98(4):620-30. doi: 10.1111/cbdd.13915, PMID 34148304.
112. Dong R, Zhang X, Liu Y, Zhao T, Sun Z, Liu P. Rutin alleviates end MT by restoring autophagy through inhibiting HDAC1 via PI3K/AKT/mTOR pathway in diabetic kidney disease. Phytomedicine. 2023 Apr;112:154700. doi: 10.1016/j.phymed.2023.154700, PMID 36774842.
113. Tao M, Zheng D, Liang X, WU D, HU K, Jin J. Tripterygium glycoside suppresses epithelial to mesenchymal transition of diabetic kidney disease podocytes by targeting autophagy through the mTOR/Twist1 pathway. Mol Med Rep. 2021;24(2):592. doi: 10.3892/mmr.2021.12231, PMID 34165172.
114. LI XY, Wang SS, Han Z, Han F, Chang YP, Yang Y. Triptolide restores autophagy to alleviate diabetic renal fibrosis through the miR-141-3P/PTEN/Akt/mTOR pathway. Mol Ther Nucleic Acids. 2017 Aug 25;9:48-56. doi: 10.1016/j.omtn.2017.08.011, PMID 29246323.
115. Yang F, QU Q, Zhao C, Liu X, Yang P, LI Z. Paecilomyces cicadae fermented *Radix astragali* activates podocyte autophagy by attenuating PI3K/AKT/mTOR pathways to protect against diabetic nephropathy in mice. Biomed Pharmacother. 2020 Sep;129:110479. doi: 10.1016/j.biopha.2020.110479, PMID 32768963.
116. Guo L, Tan K, Luo Q, Bai X. Dihydromyricetin promotes autophagy and attenuates renal interstitial fibrosis by regulating miR-155-5p/PTEN signaling in diabetic nephropathy. Bosn J Basic Med Sci. 2020;20(3):372-80. doi: 10.17305/bjbms.2019.4410, PMID 31668144.
117. Wang T, Gao Y, Yue R, Wang X, Shi Y, XU J. Ginsenoside Rg1 alleviates podocyte injury induced by hyperlipidemia via targeting the mTOR/NF-κB/NLRP3 axis. Evid Based Complement Alternat Med. 2020;2020(1):2735714. doi: 10.1155/2020/2735714, PMID 33133213.
118. Sheng H, Zhang D, Zhang J, Zhang Y, LU Z, Mao W. Kaempferol attenuated diabetic nephropathy by reducing apoptosis and promoting autophagy through AMPK/mTOR pathways. Front Med (Lausanne). 2022;9:986825. doi: 10.3389/fmed.2022.986825, PMID 36530875.
119. Wang WJ, Jiang X, Gao CC, Chen ZW. Salusin-α mitigates diabetic nephropathy via inhibition of the Akt/mTORC1/p70S6K signaling pathway in diabetic rats. Drug Chem Toxicol. 2022;45(1):283-90. doi: 10.1080/01480545.2019.1683572, PMID 31665937.
120. Zhang Y, Wang Y, Luo M, XU F, LU Y, Zhou X. Elabela protects against podocyte injury in mice with streptozocin-induced diabetes by associating with the PI3K/Akt/mTOR pathway.

Peptides. 2019 Apr;114:29-37. doi: 10.1016/j.peptides.2019.04.005, PMID 30959144.
121. WU C, MA X, Zhou Y, Liu Y, Shao Y, Wang Q. Klotho restraining Egr1/TLR4/mTOR axis to reducing the expression of fibrosis and inflammatory cytokines in high glucose cultured rat mesangial cells. Exp Clin Endocrinol Diabetes. 2019;127(9):630-40. doi: 10.1055/s-0044-101601, PMID 29890551.
122. DI Petrillo K, Coutermarsh B, Gesek FA. Urinary tumor necrosis factor contributes to sodium retention and renal hypertrophy during diabetes. Am J Physiol Renal Physiol. 2003;284(1):F113-21. doi: 10.1152/ajprenal.00026.2002, PMID 12388406.
123. Moriwaki Y, Inokuchi T, Yamamoto A, KA T, Tsutsumi Z, Takahashi S. Effect of TNF-alpha inhibition on urinary albumin excretion in experimental diabetic rats. Acta Diabetol. 2007;44(4):215-8. doi: 10.1007/s00592-007-0007-6, PMID 17767370.
124. Omote K, Gohda T, Murakoshi M, Sasaki Y, Kazuno S, Fujimura T. Role of the TNF pathway in the progression of diabetic nephropathy in KK-A(y) mice. Am J Physiol Renal Physiol. 2014;306(11):F1335-47. doi: 10.1152/ajprenal.00509.2013, PMID 24647715.
125. Karkar AM, Smith J, Pusey CD. Prevention and treatment of experimental crescentic glomerulonephritis by blocking tumour necrosis factor alpha. Nephrol Dial Transplant. 2001;16(3):518-24. doi: 10.1093/ndt/16.3.518, PMID 11239025.
126. Ramesh G, Reeves WB. TNFR2-mediated apoptosis and necrosis in cisplatin induced acute renal failure. Am J Physiol Renal Physiol. 2003;285(4):F610-8. doi: 10.1152/ajprenal.00101.2003, PMID 12865254.
127. Zandi Nejad K, Eddy AA, Glassock RJ, Brenner BM. Why is proteinuria an ominous biomarker of progressive kidney disease? Kidney Int Suppl. 2004;66(92):S76-89. doi: 10.1111/j.1523-1755.2004.09220.x, PMID 15485426.
128. Lin SL, Chiang WC, Chen YM, Lai CF, Tsai TJ, Hsieh BS. The renoprotective potential of pentoxifylline in chronic kidney disease. J Chin Med Assoc. 2005;68(3):99-105. doi: 10.1016/S1726-4901(09)70228-X, PMID 15813241.
129. Garcia FA, Pinto SF, Cavalcante AF, Lucetti LT, Menezes SM, Felipe CF. Pentoxifylline decreases glycemia levels and TNF-alpha, iNOS and COX-2 expressions in diabetic rat pancreas. Springerplus. 2014;3(1):283. doi: 10.1186/2193-1801-3-283, PMID 24991532.
130. Goicoechea M, Garcia DE Vinuesa S, Quiroga B, Verdalles U, Barraca D, Yuste C. Effects of pentoxifylline on inflammatory parameters in chronic kidney disease patients: a randomized trial. J Nephrol. 2012;25(6):969-75. doi: 10.5301/jn.5000077, PMID 22241639.
131. Sahın S, Altok K, Pasaoglu H, Omeroglu S, Derıcı B, Erten U. The protective effects of pentoxifylline on contrast induced nephropathy in rats. Akdeniz Tıp Derg. 2019;5(3):429-38.
132. Gonzalez Espinoza L, Rojas Campos E, Medina Perez M, Pena Quintero P, Gomez Navarro B, Cueto Manzano AM. Pentoxifylline decreases serum levels of tumor necrosis factor alpha interleukin 6 and C-reactive protein in hemodialysis patients: results of a randomized double-blind controlled clinical trial. Nephrol Dial Transplant. 2012;27(5):2023-8. doi: 10.1093/ndt/gfr579, PMID 21968012.
133. Varma A, Das A, Hoke NN, Durrant DE, Salloum FN, Kukreja RC. Anti-inflammatory and cardioprotective effects of tadalafil in diabetic mice. Plos One. 2012;7(9):e45243. doi: 10.1371/journal.pone.0045243, PMID 23028874.
134. Kuwabara T, Mori K, Mukoyama M, Kasahara M, Yokoi H, Saito Y. Urinary neutrophil gelatinase-associated lipocalin levels reflect damage to glomeruli proximal tubules and distal nephrons. Kidney Int. 2009;75(3):285-94. doi: 10.1038/ki.2008.499, PMID 19148153.
135. Joy SV, Scates AC, Bearelly S, Dar M, Taulien CA, Goebel JA. Ruboxistaurin a protein kinase C β inhibitor as an emerging treatment for diabetes microvascular complications. Ann Pharmacother. 2005;39(10):1693-9. doi: 10.1345/aph.1E572, PMID 16160002.
136. Dash A, Maiti R, Bandakkanavar TK, Pandey BL. Novel drug treatment for diabetic nephropathy. HK J Nephrol. 2011;13(1):19-26. doi: 10.1016/S1561-5413(11)60003-3.
137. Pham TK, Nguyen TH, Yun HR, Vasileva EA, Mishchenko NP, Fedoreyev SA. Echinochrome prevents diabetic nephropathy by inhibiting the PKC-Iota pathway and enhancing renal mitochondrial function in DB/DB mice. Mar Drugs. 2023;21(4):222. doi: 10.3390/md21040222, PMID 37103361.
138. Gorin Y, Cavaglieri RC, Khazim K, Lee DY, Bruno F, Thakur S. Targeting NADPH oxidase with a novel dual Nox1/Nox4 inhibitor attenuates renal pathology in type 1 diabetes. Am J Physiol Renal Physiol. 2015;308(11):F1276-87. doi: 10.1152/ajprenal.00396.2014, PMID 25656366.
139. Menne J, Eulberg D, Beyer D, Baumann M, Saudek F, Valkusz Z. C-C motif ligand 2 inhibition with emapticap pegol *(*NOX-E36*)* in type 2 diabetic patients with albuminuria. Nephrol Dial Transplant. 2017;32(2):307-15. doi: 10.1093/ndt/gfv459.
140. Boels MG, Koudijs A, Avramut MC, Sol WM, Wang G, Van Oeveren Rietdijk AM. Systemic monocyte chemotactic protein-1 inhibition modifies renal macrophages and restores glomerular endothelial glycocalyx and barrier function in diabetic nephropathy. Am J Pathol. 2017;187(11):2430-40. doi: 10.1016/j.ajpath.2017.07.020, PMID 28837800.
141. DE Zeeuw D, Akizawa T, Agarwal R, Audhya P, Bakris GL, Chin M. Rationale and trial design of bardoxolone methyl evaluation in patients with chronic kidney disease and type 2 diabetes: the occurrence of renal events (beacon). Am J Nephrol. 2013;37(3):212-22. doi: 10.1159/000346948, PMID 23467003.
142. DE Zeeuw D, Akizawa T, Audhya P, Bakris GL, Chin M, Christ Schmidt H. Bardoxolone methyl in type 2 diabetes and stage 4 chronic kidney disease. N Engl J Med. 2013;369(26):2492-503. doi: 10.1056/NEJMoa1306033, PMID 24206459.
143. Taylor PC. Clinical efficacy of launched JAK inhibitors in rheumatoid arthritis. Rheumatol (Oxf Engl). 2019;58 Suppl 1:17-26. doi: 10.1093/rheumatology/key225, PMID 30806707.
144. Plosker GL. *Ruxolitinib*: a review of its use in patients with myelofibrosis. Drugs. 2015;75(3):297-308. doi: 10.1007/s40265-015-0351-8, PMID 25601187.
145. Schwartz DM, Kanno Y, Villarino A, Ward M, Gadina M, O Shea JJ. JAK inhibition as a therapeutic strategy for immune and inflammatory diseases. Nat Rev Drug Discov. 2017;16(12):843-62. doi: 10.1038/nrd.2017.201, PMID 29104284.
146. Kim HO. Development of JAK inhibitors for the treatment of immune mediated diseases: kinase targeted inhibitors and pseudokinase targeted inhibitors. Arch Pharm Res. 2020;43(11):1173-86. doi: 10.1007/s12272-020-01282-7, PMID 33161563.
147. Brosius FC, Tuttle KR, Kretzler M. JAK inhibition in the treatment of diabetic kidney disease. Diabetologia. 2016;59(8):1624-7. doi: 10.1007/s00125-016-4021-5, PMID 27333885.
148. Tuttle KR, Brosius FC, Adler SG, Kretzler M, Mehta RL, Tumlin JA. JAK1/JAK2 inhibition by baricitinib in diabetic kidney disease: results from a phase 2 randomized controlled clinical trial. Nephrol Dial Transplant. 2018;33(11):1950-9. doi: 10.1093/ndt/gfx377, PMID 29481660.
149. El Kady MM, Naggar RA, Guimei M, Talaat IM, Shaker OG, Saber Ayad M. Early renoprotective effect of ruxolitinib in a rat model of diabetic nephropathy. Pharmaceuticals (Basel). 2021;14(7):608. doi: 10.3390/ph14070608, PMID 34202668.
150. Elsherbiny NM, Zaitone SA, Mohammad HM, El Sherbiny M. Renoprotective effect of nifuroxazide in diabetes-induced nephropathy: impact on NFκB oxidative stress and apoptosis. Toxicol Mech Methods. 2018;28(6):467-73. doi: 10.1080/15376516.2018.1459995, PMID 29606028.
151. Zhu M, Wang H, Chen J, Zhu H. Sinomenine improve diabetic nephropathy by inhibiting fibrosis and regulating the JAK2/STAT3/SOCS1 pathway in streptozotocin-induced diabetic rats. Life Sci. 2021 Jan 15;265:118855. doi: 10.1016/j.lfs.2020.118855, PMID 33278392.
152. Gholami M, Moallem SA, Afshar M, Amoueian S, Etemad L, Karimi G. Teratogenic effects of silymarin on mouse fetuses. Avicenna J Phytomed. 2016;6(5):542-9. PMID 27761424.
153. Winiarska A, Knysak M, Nabrdalik K, Gumprecht J, Stompor T. Inflammation and oxidative stress in diabetic kidney disease: the targets for SGLT2 inhibitors and GLP-1 receptor agonists. Int J Mol Sci. 2021;22(19):10822. doi: 10.3390/ijms221910822, PMID 34639160.

154. Yang Y, Lei Y, Liang Y, FU S, Yang C, Liu K. Vitamin D protects glomerular mesangial cells from high glucose-induced injury by repressing JAK/STAT signaling. Int Urol Nephrol. 2021;53(6):1247-54. doi: 10.1007/s11255-020-02728-z, PMID 33942213.
155. Navarro Gonzalez JF, Mora Fernandez C, Muros DE Fuentes M, Garcia Perez J. Inflammatory molecules and pathways in the pathogenesis of diabetic nephropathy. Nat Rev Nephrol. 2011;7(6):327-40. doi: 10.1038/nrneph.2011.51, PMID 21537349.
156. LI HY, Lin HA, Nien FJ, WU VC, Jiang YD, Chang TJ. Serum vascular adhesion protein-1 predicts end-stage renal disease in patients with type 2 diabetes. Plos One. 2016;11(2):e0147981. doi: 10.1371/journal.pone.0147981, PMID 26845338.
157. Qian Y, LI S, YE S, Chen Y, Zhai Z, Chen K. Renoprotective effect of rosiglitazone through the suppression of renal intercellular adhesion molecule-1 expression in streptozotocin-induced diabetic rats. J Endocrinol Invest. 2008;31(12):1069-74. doi: 10.1007/BF03345654, PMID 19246972.
158. Rubio Guerra AF, Vargas Robles H, Lozano Nuevo JJ, Escalante Acosta BA. Correlation between circulating adhesion molecule levels and albuminuria in type-2 diabetic hypertensive patients. Kidney Blood Press Res. 2009;32(2):106-9. doi: 10.1159/000210554, PMID 19342863.
159. DE Zeeuw D, Renfurm RW, Bakris G, Rossing P, Perkovic V, Hou FF. Efficacy of a novel inhibitor of vascular adhesion protein1 in reducing albuminuria in patients with diabetic kidney disease (ALBUM): a randomised placebo-controlled phase 2 trial. Lancet Diabetes Endocrinol. 2018;6(12):925-33. doi: 10.1016/S2213-8587(18)30289-4, PMID 30413396.
160. Wada J, Makino H. Inflammation and the pathogenesis of diabetic nephropathy. Clin Sci (Lond). 2013;124(3):139-52. doi: 10.1042/CS20120198, PMID 23075333.
161. Giunti S, Barutta F, Perin PC, Gruden G. Targeting the MCP-1/CCR2 system in diabetic kidney disease. Curr Vasc Pharmacol. 2010;8(6):849-60. doi: 10.2174/157016110793563816, PMID 20180766.
162. Sayyed SG, Hagele H, Kulkarni OP, Endlich K, Segerer S, Eulberg D. Podocytes produce homeostatic chemokine stromal cell-derived factor-1/CXCL12 which contributes to glomerulosclerosis podocyte loss and albuminuria in a mouse model of type 2 diabetes. Diabetologia. 2009;52(11):2445-54. doi: 10.1007/s00125-009-1493-6, PMID 19707743.
163. Enevoldsen FC, Sahana J, Wehland M, Grimm D, Infanger M, Kruger M. Endothelin receptor antagonists: status quo and future perspectives for targeted therapy. J Clin Med. 2020;9(3):824. doi: 10.3390/jcm9030824, PMID 32197449.
164. Wang Y, Chen S, DU J. Bosentan for treatment of pediatric idiopathic pulmonary arterial hypertension: state of the art. Front Pediatr. 2019 Jul 23;7:302. doi: 10.3389/fped.2019.00302, PMID 31396496.
165. Schlaich MP, Bellet M, Weber MA, Danaietash P, Bakris GL, Flack JM. Dual endothelin antagonist aprocitentan for resistant hypertension (Precision): a multicentre blinded randomised parallel-group phase 3 trial. Lancet. 2022;400(10367):1927-37. doi: 10.1016/S0140-6736(22)02034-7, PMID 36356632.
166. Murugesan N, GU Z, Fadnis L, Tellew JE, Baska RA, Yang Y. Dual angiotensin II and endothelin a receptor antagonists: synthesis of 2 substituted N-3-isoxazolyl biphenylsulfonamides with improved potency and pharmacokinetics. J Med Chem. 2005;48(1):171-9. doi: 10.1021/jm049548x, PMID 15634011.
167. Zhao Q, Guo N, Chen J, Parks D, Tian Z. Comparative assessment of efficacy and safety of ambrisentan and bosentan in patients with pulmonary arterial hypertension: a meta analysis. J Clin Pharm Ther. 2022;47(2):146-56. doi: 10.1111/jcpt.13481, PMID 34319626.
168. Persson BP, Rossi P, Weitzberg E, Oldner A. Inhaled tezosentan reduces pulmonary hypertension in endotoxin-induced lung injury. Shock. 2009;32(4):427-34. doi: 10.1097/SHK.0b013e31819e2cbb, PMID 19197226.
169. Iglarz M, Binkert C, Morrison K, Fischli W, Gatfield J, Treiber A. Pharmacology of macitentan an orally active tissue targeting dual endothelin receptor antagonist. J Pharmacol Exp Ther. 2008;327(3):736-45. doi: 10.1124/jpet.108.142976, PMID 18780830.