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REVIEW ARTICLE

Innovative approaches in kidney disease management: Advances in therapeutics and treatment strategies

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Abstract

The health system is burdened by kidney disease (KD), which has considerable economic consequences. The aging population and the rise in Type 2 diabetes and hypertension are the main contributing causes. KD is also associated with an increased risk of cardiovascular diseases (CVDs) morbidity, early mortality, and reduced quality of life. Recent studies estimate that more than 850 million people worldwide are affected by kidney-related illnesses each year. Of these, about 3.9 million individuals are going through dialysis or kidney transplantations, neither of which provides an ultimate solution. Alternative therapeutic approaches through medications include the use of angiotensin-converting enzyme inhibitors and Angiotensin II receptor blockers, renin inhibitors, anti-inflammatory medicines, and bioactive phytocompounds isolated from several plants. Plants contain numerous bioactive compounds that are thought to provide a variety of health benefits, including potential nephroprotective properties. In this review, recent advancements in kidney disease (KD) research will be highlighted, including newly identified causes, renal pathophysiological alterations, and current therapeutic approaches.

Keywords: Kidney disease; Phytocompounds; Nephroprotective; Anti-inflammatory

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1. Introduction

Acute kidney injury (AKI) is a syndrome characterized by reduced urine production and the accumulation of nitrogen metabolism end products, such as urea and creatinine in renal tubules.[1] At the initial phase of injury and inflammation, circulating immune cells (T- and B-cells) infiltrate the kidney, drawn in by cytokines, chemokines, and damage-associated molecular patterns (DAMPs) generated by wounded cells. DAMPs contribute to a pro-fibrotic environment by interacting with activated monocytes/macrophages, damaged tubular epithelial cells (TECs), and endothelial cells. This environment stimulates pericytes to proliferate and differentiate into myofibroblasts, which causes extracellular matrix (ECM) protein deposition, renal fibrosis, and progression to chronic kidney disease (CKD). TECs may have a pro-fibrotic phenotype and become

atrophic as a result of aberrant repair pathways. Pro-fibrotic cytokines, including connective tissue growth factor and transforming growth factor-β (TGF-β), may be produced by G2/M-arrested TECs through activation of JNK signaling. Cell cycle arrest may dictate the course of damage, whereas favorable cell cycle events may determine the healing. Dysregulated and inefficient tubular repair has been associated with the converging of tubular cells toward a pro-fibrotic and senescent phenotype, sustained inflammation, and ECM deposition.[2,3]

It has been noted that regardless of the cause, patients with AKI are more likely to develop CKD, end-stage renal disease (ESKD), and premature mortality.[4] At present, 850 million individuals are suffering from KD and its related illnesses, including the 3.9 million receiving regular dialysis or kidney transplantation.[5] Globally, the anticipated number of individuals with diabetes in 2015 was 415 million, or 8.8% of the total population. This is more than double the 4.6% (151 million) estimated in 2000, and by 2040, the figure is predicted to rise to 10.4% (642 million). One well-known example of a chronic multisystemic illness linked to an increased risk factor of CVD is CKD. According to clinical and experimental evidence, CKD increases oxidative stress and promotes an inflammatory state, both of which are critical factors in the development of CVD in uremia.[6,7]

CKD is marked by vasculopathy, renal interstitial fibrosis, tubular atrophy, and glomerulosclerosis, leading to impaired kidney regeneration. Renal fibrosis is histologically indicative of the onset of KD, albeit the underlying mechanisms are yet unknown.[8] Over the last few decades, research on animals and molecules has expanded our knowledge of the pathophysiology of AKI, identifying oxidative stress, endothelial damage, mitochondrial injury, and innate immunity as primary causes.[9] Oxidative stress is thought to be a major factor in the development of endothelial impairment, as excessive reactive oxygen species (ROS) activate intracellular signaling pathways, such as mitogen-activated protein kinase (MAPK). Furthermore, the uremic endothelium exhibits a proinflammatory phenotype, characterized by increased synthesis and expression of adhesion molecules, which have been found to be important factors in endothelial activation and damage.[7] Many signaling pathways that maintain homeostasis are routinely activated by the creation of reactive species. However, the excessive generation of reactive species can be highly detrimental. As mitochondrial damage increases, the electron transport chain becomes less effective, which also results in a drop in ATP production and an increased ROS creation. Impaired mitochondrial respiration is an indication of an imbalanced aerobic metabolism and increased oxidative stress in patients receiving hemodialysis and those with CKD.[10] The etiology of CKD is influenced by hampered cellular antioxidant mechanisms, which also affect signaling processes that lead to senescence and death of renal cells, renal fibrosis, and reduced renal cell regeneration.

This review gives an update on the discovery of new antioxidant drugs for CKD and discusses the sources of ROS, transcription factors, and signaling mechanisms impacted by the oxidative stress-related pathway during the development of renal fibrosis. Ongoing research worldwide is exploring various causes of KD and contemporary prevention measures (Figure 1), which are outlined in this review article.

2. Newly identified causes of CKD

2.1. Mitochondrial dysfunction

Despite the fact that mitochondria have long been associated with the pathobiology of AKI, interest in how this cellular organelle contributes to the development of AKI and CKD is expanding. Mitochondrial fragmentation has been related to cell loss in the kidney and other organs. The mitochondrial fission protein dynamin-related protein 1 (DRP1), which constricts and cleaves mitochondria and induces fragmentation, was specifically deleted in the proximal tubules, preventing renal ischemia-reperfusion damage and promoting epithelial recovery. Furthermore, DRP1 deletion in the proximal tubules after ischemia-reperfusion slowed the development of kidney damage and fibrosis, suggesting that DRP1 in the proximal tubules increases the kidneys' vulnerability to AKI and that activation of the protein contributes to maladaptive repair over time.[11,12]

2.2. Cell death pathway

The control of cell death is another crucial function of mitochondria, in addition to their well-known involvement in cellular metabolism. Recent research suggests that mitochondrial permeability transition is also an important mediator of AKI and the subsequent progression to CKD. These pathways include necroptosis, ferroptosis, and apoptosis. Studies have shown that the absence of caspase-3, a key pro-apoptotic enzyme, leads to significant kidney abnormalities in mice, highlighting the critical role of tubular cell death in AKI. Recent research suggests that ischemic conditions lead to reduced microvascular loss in mice but exacerbate tubular damage, accompanied by elevated levels of the necroptosis marker, receptor-interacting protein kinase 3 (RIPK3).[13] Ischemia induces apoptosis by causing oxidative stress, mitochondrial dysfunction, and the production of

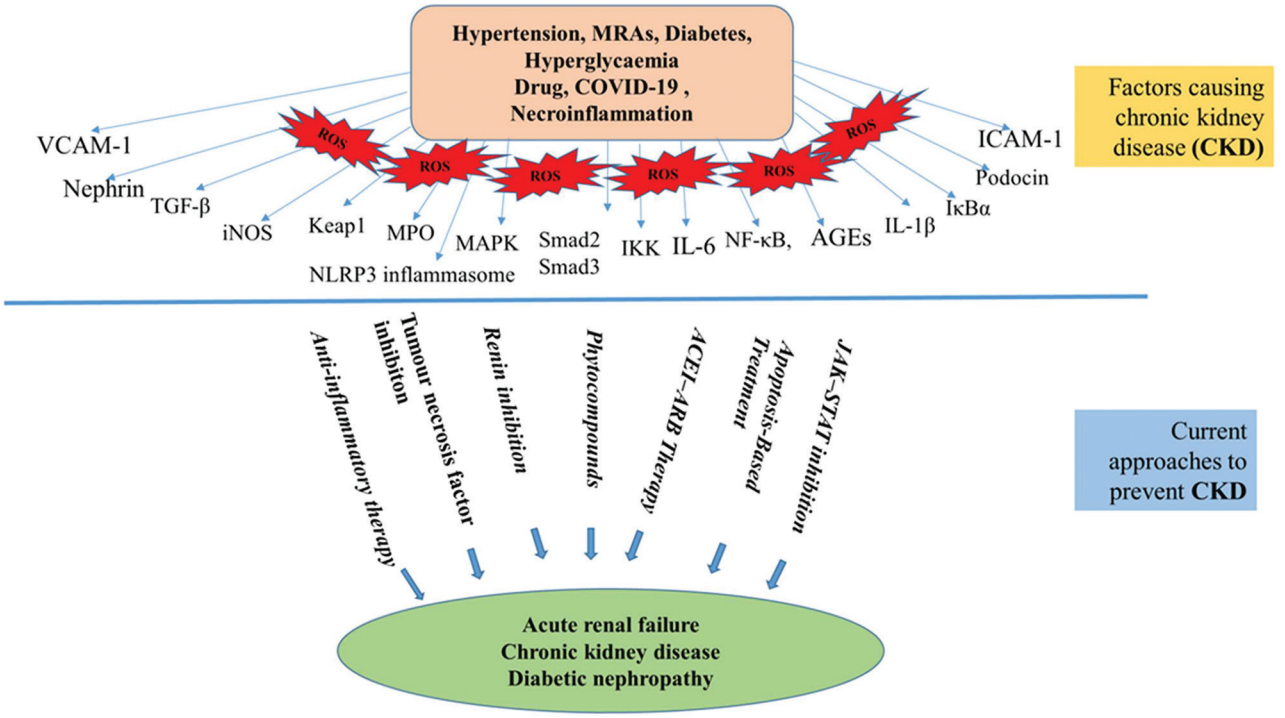

Figure 1. Recent advancement in the causative factors and preventive strategies for kidney disease.
Abbreviations: MRAs: Mineralocorticoid receptor antagonists; VCAM-1: Vascular cell adhesion protein 1; ROS: Reactive oxygen species; TGF-β: Transforming growth factor-β; KEAP1: Kelch-like ECH associated protein 1; MPO: Myeloperoxidase; SMAD2: Suppressor of mothers against decapentaplegic 2; SMAD3: Suppressor of mothers against decapentaplegic 3; IKK: Ikappa B kinase; IL-6: Interleukin-6; NF-κB: Nuclear factor-kappa B; AGEs: Advanced glycation end-products; IL-1β: Interleukin-1β; IκBα: Ikappa B-alpha; ICAM-1: Intercellular adhesion molecule 1; NLRP3: NLR family pyrin domain containing 3; ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin II receptor blocker; JAK: Janus kinase; STAT: Signal transducer and activator of transcription.

pro-apoptotic proteins. Reperfusion triggers a series of reactions, including immune cell activation, inflammation, and the production of ROS. Apoptosis is particularly likely to occur in proximal tubular cells during renal ischemia-reperfusion injury (IRI). These cells, which participate in solute reabsorption, exhibit significant metabolic activity. Apoptosis is the final outcome of oxidative stress, ATP depletion, and mitochondrial dysfunction experienced by proximal tubular cells during IRI. As apoptotic cells emit DAMPs, immune cells get activated, and proinflammatory cytokines are produced, which ultimately cause damage to renal tissue.[14]

2.3. Inflammation

Necroinflammation, in which inflammation and kidney damage are both amplified in an auto-amplification cycle, is a defining feature of controlled necrosis. Necroinflammation can be initiated by a few necrotic cells that trigger the innate immune system. This can lead to further cell necrosis and inflammation, which can ultimately lead to organ failure. Damaged cells that survive renal cell injury also release different kinds of proinflammatory cytokines and chemokines, which, in conjunction with resident macrophages, dendritic cells, and the innate immunity response from infiltrating neutrophils, lymphocytes, and monocytes, intensify the inflammatory milieu. As a result, inflammation plays a crucial role in the pathophysiologic component of AKI.[15,16]

2.4. Acute respiratory distress syndrome (ARDS) related AKI

AKI is observed in 35% – 50% of patients who develop ARDS, and it dramatically increases intensive care unit mortality by about twofold. Renal injury can be caused or worsened by several factors, such as ARDS and its associated mechanical breathing procedures. These factors can be broadly categorized into five groups which include hyperinflammation, acid-base dysregulation, poor gas exchange (hypoxia/hypercapnia), hemodynamic consequences, and neurohormonal impacts. Immunosuppressed patients, especially those with T cell-mediated immunity dysfunction, are more susceptible to severe viral infections due to a reduced immune system. Depending on the specific situation and severity of the

sickness, immunosuppression in transplant recipients with suspected or confirmed COVID-19 should be altered promptly. After the onset of ARDS, significant AKI frequently manifests in COVID-19 patients, indicating that lung-kidney crosstalk is the primary mechanism causing kidney injury.[17,18]

2.5. Role of SARSCoV2 in KD

Angiotensin-converting enzyme 2 (ACE2), a homolog of ACE, reduces vasoconstriction induced by the renin-angiotensin system by converting Angiotensin II to angiotensin 1 – 7. There are two types of ACE2: membrane-bound ACE2 and soluble ACE2. SARS-CoV-2 attaches to ACE2 on the host cell membranes. The ability of coronaviruses to enter cells depends on their ability to attach to cellular receptors and prime their S proteins for entry by host cell proteases. As a result, the activity of the protease transmembrane protease, serine 2 (TMPRSS2) to cleave the viral spike protein and the expression of ACE2, are essential for cell invasion. Both podocytes and the apical brush borders of the proximal tubules in the kidneys express ACE2. ACE is expressed in renal endothelial cells, whereas ACE2 is not. Recent human tissue RNA-sequencing data show that the expression of ACE2 in kidney tissue is about 100 times higher than in pulmonary tissue. The proximal tubules of the kidney have been shown to express TMPRSS2.[19] Antibodies against ACE2 are produced when ACE2 binds to the SARS-CoV-2 spike protein, causing a conformational shift in proteins that serve as a target for autoantibody development. After antigen-presenting cells process complexes of SARS-CoV-2 and soluble ACE2, antibodies may cause type 2/3 hypersensitivity reactions, in addition to Type 4 hypersensitivity reactions. Type 2 hypersensitivity responses during SARS-CoV-2 infection trigger the production of immunoglobulin M against ACE2, which targets ACE2 in kidney cells and causes renal impairment.[20] Recent research revealed that SARS-CoV-2 entered host cells through the novel CD147-spike protein pathway. The transmembrane glycoprotein CD147, which is widely expressed, has been linked to numerous kidney illnesses, including CKD. It is significantly expressed on inflammatory cells and proximal TECs.[21,22] According to Legrand *et al.*, the enhanced production of inflammatory cytokines by resident and immune kidney cells is likely a factor contributing to tissue damage in COVID-19 patients. In COVID-19, nuclear factor erythroid 2-related factor 2 (Nrf2) and its downstream signaling components are likewise suppressed in the lungs. Inflammatory mediators such as tumor necrosis factor (TNF) and FAS can directly harm renal endothelial and epithelial cells by binding to specific receptors they express. These associations, observed in laboratory models of sepsis, are supported by plasma cytokine levels in patients with sepsis-associated AKI.[23] Human COVID-19 infection is caused by the interaction of the viral spike protein's receptor-binding domain with the cell surface ACE2. The spike protein is then cleaved by proteases, such as TMPRSS2, in a proteolytic manner. When the virus interacts with CD147, which is expressed on the proximal convoluted tubules of the nephron and inflammatory cells; it can cause acute tubular necrosis, collapsing glomerulopathy, protein leakage from Bowman's capsule, and mitochondrial dysfunction.[24]

2.6. Impaired renal reflex in AKI

The pathophysiology of renal disorders is thought to be influenced by renal sympathetic nerve activity. The intrarenal release of adenosine, triggered by tissue ischemia, increases the activity of both afferent renal sensory neurons and efferent renal sympathetic nerve activity. Equally significant in the etiology of AKI is the effects of efferent RSNA, which include decreased renal blood flow and oxygen delivery, as well as increased renal workload. In hypotensive and hypovolemic conditions, an elevation in RSNA causes acute renal vasoconstriction. This results in glomerulotubular dysfunction, hormonal changes, and the development of renal ischemia.[25] In contrast to angiotensin-converting enzyme inhibitor (ACEI)/angiotensin II receptor blockers (ARB) monotherapy, short-term use of mineralocorticoid receptor antagonists (MRAs) in combination with ACEIs/ARBs was not associated with a lower risk of cardiovascular or renal outcomes in patients with diabetic KD and hypertension. A real-world clinical problem for MRA-ACEI/ARB combination therapy is indicated by the risk of hyperkalemia and the brief duration of the combination medication. Numerous pathophysiological conditions, including diabetes, hypoxia, ureteral blockage, cirrhosis, and renal IRI, have been linked to this defective inhibitory renorenal reflex.[26] Nitric oxide (NO), which functions as both a neurotransmitter and neuromodulator, is one of the several neurotransmitters in the brain that alter sympathetic nerve activity. Inducible nitric oxide synthase (iNOS) and neuronal NO synthase (nNOS)-induced endogenous NO synthesis seem to affect blood pressure and sympathetic nervous system activity differently. This is thought to be caused, at least in part, by the differential release of neurotransmitters in the rostral ventrolateral medulla, including inhibitory gamma-aminobutyric acid and sympatho-excitatory glutamate. Cyclic 3′-5′ guanosine monophosphate-dependent processes are suggested in the control of neuronal activity by microinjection of exogenous NO. The inhibition of Angiotensin II release also mediates

the effects of NO system activation within the central sympathetic nervous system.[27]

3. Current therapeutic approach of CKD

3.1. Combining ACEI and ARB therapy

According to recent studies, since the RAS is clearly involved in the development of renal disease, more complete RAS blockade may be able to halt its progression. In contrast to ACEI/ARB monotherapy, short-term use of MRAs, such as spironolactone or eplerenone, in combination with ACEIs/ARBs was not associated with a lower risk of cardiovascular and renal outcomes in patients with diabetic KD and hypertension. Given the short duration of combination therapy and the risk factor of hyperkalemia, MRA-integrated ACEI/ARB combination therapy may face practical therapeutic challenges.[26,28] To investigate this, several trials investigating the combination of an ACEIs and ARBs have been performed. Although they have distinct mechanisms of action, ACEIs and ARBs both disrupt the RAS. ACEIs inhibit Angiotensin-I from converting to Angiotensin II, whereas ARBs prevent Angiotensin II from binding to Angiotensin II Type 1 receptors. Analyses of ACEIs and other ARBs have revealed that they are equally effective in reducing blood pressure.[29] By maintaining peritubular capillary perfusion through efferent arteriolar vasodilation and boosting the renal medullary plasma flow by decreasing the filtration fraction, ACEIs/ARBs could mitigate tubular damage following AKI insults. Angiotensin II blockade has been demonstrated to lessen the development of acute tubular necrosis or damage as well as tubular ischemia. In addition, ACEIs/ARBs are advised to slow the course of kidney deterioration in diabetic nephropathy. In addition, ACEIs/ARBs lower CVD-related mortality, such as myocardial infarction and congestive heart failure. The use of ACEIs/ARBs is generally supported by evidence, as they protect the kidneys and heart and lower all-cause mortality. Our present meta-analysis findings support their timely use following AKI and consistent with previous reports. Profibrotic pathways may directly damage essential organs if the RAAS is activated, and AKI has a major effect on the functioning of injury/repair pathways in distant organs. Following AKI and CKD, we hypothesize that using ACEIs/ARBs may enhance organ function and avoid maladaptive repair.[30-32] The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET), which included 25,920 individuals with vascular diseases and a higher risk of diabetes, evaluated the benefits of ACEI ramipril, ARB telmisartan, and their combination. The majority of patients included in ONTARGET did not exhibit microalbuminuria and/or macroalbuminuria at baseline. Therefore, it was not possible to determine the renal benefit of combined ACEI/ARB treatment for patients with proteinuria. Due to hypotensive symptoms, 784 participants (mostly those on combination therapy) permanently stopped receiving randomized therapy throughout the research. Compared to patients receiving monotherapy, the combination treatment group had a considerably higher number of patients reaching the primary renal outcome of dialysis, doubling of serum creatinine, or death. Acute renal failure was the primary cause of many dialysis episodes, and it was more common in individuals with normotension. These unsatisfactory but not totally unexpected findings highlight the safety concerns related to ACEI/ARB treatment.[33] The abrupt transition to sodium-glucose cotransporter-2 inhibitors and MRAs for reducing albuminuria, followed by a return to ACEIs and ARBs, resulted in greatly reduced hyperkalemia and potassium levels, as well as a dramatically lowered the urinary albumin-to-creatinine ratio when dapagliflozin and eplerenone were taken as adjuvants to ACEIs or ARBs. These recent trials imply that dapagliflozin with eplerenone is a desirable combination to help individuals with CKD reduce the course of their illness.[34] RAS blocker medications increased the risk of hyperkalemia, hypotension, and cough, but they also improved the outcomes for patients with non-dialysis CKD. ACEIs were more likely than ARBs and other antihypertensive drugs to be the most effective therapy for renal events, cardiovascular outcomes, and causes of mortality in patients with diabetic KD, and non-dialysis CKD. ARBs outperformed ACEIs in preventing the risk of cardiovascular and renal events, but they were less effective than ACEIs in lowering all-cause mortality.[35-37]

3.2. RAS and renin inhibition

ACEIs and ARBs are RAS inhibitors that slow the progression of mild to severe CKD. According to some research, discontinuing RAS inhibitors in individuals with severe chronic renal disease may result in an increase in estimated glomerular filtration rate or a slowing of its decline.[38] Evidence does not support the combination therapy of aliskiren and losartan among non-diabetic CKD patients generally, and aliskiren does not provide extra renoprotection over a 144-week period in individuals with non-diabetic KD. However, KD responders could potentially benefit from direct renin inhibition, making it a more targeted treatment option for specific subgroups of CKD patients, based on some positive short-term outcomes.[39] In particular, proinflammatory chemicals and stress hormones seem to increase the synthesis of kynurenine and its downstream metabolites, which may affect insulin action and favor the onset of diabetes mellitus and its complications, including nephropathy.

Progressive renal insufficiency has been associated with decreased tryptophan levels and kynurenine accumulation due to inflammation and impaired kidney function in diabetic individuals. Proteinuria and albuminuria are signs of several kidney illnesses, and a few clinical and experimental studies have looked into the potential link between the kynurenine pathway and these conditions. Kynurenine aminotransferases are the enzymes responsible for converting kynurenine into its downstream metabolites, and RAS inhibitors can reduce their activity, hence reducing the synthesis of kynurenic acid in kidney homogenates. These findings could be clinically significant because kynurenic acid has been linked to the extent of renal function loss in patients with kidney illness.[40] However, recent research has shown that RAS inhibitors may cause common adverse effects such as anemia, hyperkalemia, and functional renal insufficiency.[41]

3.3. Anti-inflammatory therapy

Renal failure in individuals with diabetes and inflammation has long been linked. Growing evidence from both animal and clinical trials suggests that endothelin Type A receptor antagonists may have a role in the treatment of diabetic renal diseases (DRD). Vasoconstriction, mesangial proliferation, podocyte damage, inflammation, and fibrosis are all linked to increased renal endothelin expression in DRD. In DRD patients, the expression of endothelial adhesion molecules such as intercellular adhesion molecule 1 (ICAM-1), vascular adhesion protein 1 (VAP-1), and vascular cell adhesion protein 1 (VCAM-1) is increased, and this increase is associated with the severity of the illness. These molecules are crucial for leukocyte adhesion to the endothelium; therefore, blocking them may affect leukocyte trafficking and reduce inflammation in DRD.[42]

3.4. TNF inhibition

The results are consistent with previous research suggesting that in diabetes, hyperglycemia-induced formation of advanced glycation end-products (AGEs) triggers macrophage production of TNF. However, it is unknown whether TNF or its receptors play harmful functions in the development of KD and diabetic nephropathy. TNF receptor-deficient animals treated with TNF-neutralizing antibodies have lessened disease severity in experimental rodent models of renal disease.[43] Despite anti-TNF drugs being used clinically for more than 20 years, few studies have looked into their clinical activity in renal illness. Such studies have been limited in size and mostly concentrated on focal segmental glomerulosclerosis and lupus nephritis, leaving their potential involvement in various types of CKD development largely unanswered.

3.5. Janus kinase inhibitors and signal transducer and activator of transcription (JAK/STAT) inhibition

JAK and STAT are important intracellular mediators of growth hormone, erythropoietin, pro-epidermal growth factor, and inflammatory cytokines such as interleukin(IL)-6, IL-23, IL-12, interferon, and its cognate receptor.[44] According to recent clinical trials, autoimmune inflammatory diseases such as rheumatoid arthritis and ulcerative colitis can be effectively treated with JAK inhibitors such as tofacitinib and baricitinib. In diabetic KD, the JAK/STAT signaling pathway and the documented clinical anti-inflammatory activity of JAK inhibitors have prompted a Phase II investigation to assess their clinical effectiveness in renal illness. In this trial, patients with proteinuria in diabetic KD who were already on ACEIs and ARBs were treated with the JAK1 and JAK2 inhibitor baricitinib for 24 weeks. The results showed a 30 – 40% reduction in albuminuria with baricitinib treatment. However, a side effect associated with this class of drugs – decreased hemoglobin level – was observed. The extent to which these effects on albuminuria decreased translate into long-term advantages for renal function and mortality remains to be determined.[45,33]

3.6. Apoptosis-based treatment strategies in AKI

Recent research indicates that a variety of pathways contribute to both apoptosis and programmed necrosis-induced cell death following apoptosis, including in AKI. Suppressing both processes may be necessary to completely avoid AKI. This is noteworthy because caspase inhibitors may affect autophagy and proinflammatory necroptosis, two other processes involved in cell death and survival. Phosphorylation and activation of p53 have a major function in the pathogenesis of vancomycin-induced AKI, as well as nephrotoxicity caused by folic acid, aristolochic acid, and cisplatin. Ferroptosis, cell cycle arrest, autophagy, metabolism, fibrosis, and both necrotic and apoptotic cell death are among the processes in which p53 is implicated in the kidney. Based on experimental studies, the protection against ischemia and cisplatin-induced AKI is due to the pharmacological suppression or proximal tubule-specific p53 deletion.[46,47] The p53 gene is targeted by a small interfering RNA known as teprasiran, and in a randomized Phase 2 clinical trial, teprasiran provided protection against AKI in high-risk, on-pump patients undergoing heart surgery.[48]

3.7. Phytomedicinal therapeutic approach of KD

Phytocompounds are naturally occurring groupings of different substances that are present in plants and fruits that have several health-beneficial effects, including anti-

inflammation, anti-oxidative, anti-diabetic, anticancer, and nephroprotective action. Phytocompounds, including flavonoids, have the ability to both directly and indirectly reduce renal damage. Significant biological benefits of flavonoids in CKD include reducing oxidative stress, immunological modulation, antioxidant actions, anti-inflammation, anti-apoptosis, gut microbiota regulation, anti-diabetic, and antihypertensive; they also help to relieve renal fibrosis.[49] In addition, they serve as intermediaries for the activation of the Nrf2 antioxidant action, which lowers oxidative stress.[50]

3.7.1. Troxerutin

Troxerutin, a derivative of the naturally occurring bioflavonoid and found in tea and coffee. The ability of troxerutin to reduce drug-induced nephrotoxicity has been investigated in earlier research. Troxerutin reduces the oxidative stress induced by cisplatin and methotrexate by inhibiting lipid peroxidase and nicotinamide adenine dinucleotide phosphate oxidase 1 (NOX-1), restoring superoxide dismutase (SOD), GSH, and glutathione peroxidase (GPx) levels, and activating the Nrf2/HO-1 signaling pathway.[51] Long-term administration of 2,2,4,4-tetrabromodiphenyl ether (PBDE-47) increased Kelch-like ECH associated protein 1 (KEAP1) levels, leading to Nrf2 ubiquitination and degradation, which in turn decreased Nrf2 activity and its downstream genes in the kidneys of mice, including catalase, GPx, SOD, and heme oxygenase 1 (HO-1). Nevertheless, troxerutin enhanced Nrf2 activity, prevented the negative effects of PBDE-47 and partially mimicking the action of carbobenzoxy-l-leucyl-l-leucinal (MG132). In the liver of mice, PBDE-47 was found to increase caspase-3 action and the levels of B-cell lymphoma 2 (Bcl-2)-associated X (Bax) and Bcl-2.[52] Activated TGF-β has been linked to the pathogenesis of diabetic KD. TGF-β triggers receptor activation through autocrine and paracrine pathways, initiating a signaling cycle that ultimately regulates the production of ECM, leading to the impaired mesangial cell function. As nephropathy progresses, TGF-β builds up in mesenchymal cells and influences the synthesis of ECM proteins, such as collagen I and collagen II. TGF-β inhibits E-box repressors like δEF1 and SMAD interacting protein 1 (SIP1), which regulate collagen gene expression. The role and target of certain kidney-dwelling microRNAs, such as miR-192, miR-194, miR-204, and miR-215, in the setting of nephropathy have received significant attention. Since miR-192 has been shown to target SIP1, the low levels of SIP1 observed in diabetics may validate the interaction between elevated TGF-β and miR-192, leading to low levels of SIP1 in renal tissue. Troxerutin's effects on the kidney in a diabetic rat model appear to be mediated by decreased levels of miR-192, a crucial miRNA involved in the development and exacerbation of nephropathy, and the increase of SIP1. Further research is required to assess troxerutin's effects on collagen levels and ECM proteins, to evaluate its potential as a natural preventive component that can help avoid renal problems[53] Similarly, research has found that troxerutin may reduce cisplatin-induced kidney cell death in rats by increasing microtubule-associated protein 4 (MAP4) expression and activating the PI3K/AKT signaling pathway, one of the most effective intracellular pathways for enhancing cell survival.[54] In addition, troxerutin has been demonstrated to prevent renal damage caused by drug-induced cytotoxicity in rat models by increasing the antioxidant defense system and reducing lipid peroxidation.

3.7.2. Fisetin

Fisetin, a flavonoid is isolated from a variety of fruits, vegetables, seaweeds, and persimmons, as well as strawberries, apples, and onions. After being given orally to mice, it can penetrate the blood-brain barrier and accumulate in the brain. Fisetin is rapidly bio-transformed through conjugative metabolism, mostly by glucuronidation, sulfation, and methylation in the liver, and is eliminated through urine and feces. Cytochrome P450 enzymes are among the Phase I and II metabolic enzymes involved in the metabolic process. *In vitro* research demonstrated that fisetin, like other flavonoids, inhibits a number of cytochrome P450 enzymes, potentially leading to drug interactions when combined with other medications. Fisetin inhibits myeloperoxidase (MPO) activity, inflammatory cytokines, and renal production of iNOS, thereby protecting the kidney from drug-induced renal impairment.[55] In the context of ureteric obstruction, TGF-β is essential for cell development, proliferation, differentiation, apoptosis, immunological response, and renal fibrosis. TGF-β1 binds to its receptor, TβRII, causing phosphorylation of TβRI and activation of TGF-β1 downstream effectors, including suppressor of mothers against decapentaplegic (SMAD). Canonical pathway involves receptor-regulated SMADs (R-SMADs), such as SMAD2/3, which are both overexpressed in human fibrotic kidneys, and responsible for TGF-β1 signaling transduction. Non-canonical SMAD-independent pathways, including Rho-like GTPase, PI3K/AKT, Jun N-terminal kinases (JNKs), and MAPK, also regulate gene transcription, promoting apoptosis and the epithelial-to-mesenchymal transition (EMT). In experimental models, fisetin injections (25 mg/kg) administered intraperitoneally one hour prior to surgery and every other day for seven days. In addition, fisetin pretreatment (40 μM) dramatically decreased TGF-β1-

induced phosphorylation of SMAD2/3 in human kidney-2 (HK-2) cells. By modifying TGF-β1/SMADd3 and STAT3 signaling, fisetin helps to improve kidney fibrosis.[56,57] Fisetin also reduces the release of inflammatory cytokines, AGEs, ROS, and NLR family pyrin domain containing 3 (NLRP3) inflammasome – factors associated with diabetic nephropathy. When the NLRP3 inflammasome is activated in mice, podocyte proteins such as nephrin and podocin are lost, accompanied by mitochondrial dysfunction. Tubular injury in animals has been linked to increased high glucose-induced EMT and the involvement of SMAD3, p38 MAPK, extracellular signal-regulated kinase 1 (ERK1), and ERK2 signaling pathways. Fisetin treatment reduced the expression of fibronectin, collagen, and vascular endothelial growth factor A (VEGFA) while increasing matrix metalloproteinases 2/9. This was primarily caused by inactivating the TGF-β/SMAD2/3 pathways, which inhibits the production of ECM in the kidney. Both *in vitro* and *in vivo* experiments demonstrated that fisetin effectively protects against kidney fibrosis.[58] Fisetin shows significant potential as a senolytic medication with a variety of therapeutic applications, although human data remain limited currently. Carefully supervised clinical investigations are necessary to demonstrate whether fisetin's beneficial and senolytic properties can be translated into human use. According to a recent cohort study sub-analysis, serum levels of senescence-associated secretory phenotype factors, MMP-3 and MMP-9, platelet-derived growth factor AA, IL-6 and IL-8, monocyte chemoattractant protein-1 (MCP-1), and growth differentiation factor 11 and 15, dropped between baseline and follow-up visit in healthy individuals who self-dosed with 100 mg/day of fisetin.[59] (Figure 2).

3.7.3. Kaempferol

Kaempferol, a flavonoid widely distributed in vegetables and fruits, including broccoli, tea, and grapes, exhibits antioxidant and anti-inflammatory properties. In HK-2 cells, lipopolysaccharide (LPS) upregulated the production of TNF-α and IL-1β, demonstrating its ability to induce inflammation. However, the administration of kaempferol considerably decreased the LPS-induced apoptosis in HK-2 cells.[60] LPS also induced STAT3 and NF-κB, which subsequently increased procalcitonin expression, a validated blood biomarker in septic patients. Kaempferol played a crucial anti-inflammatory role in

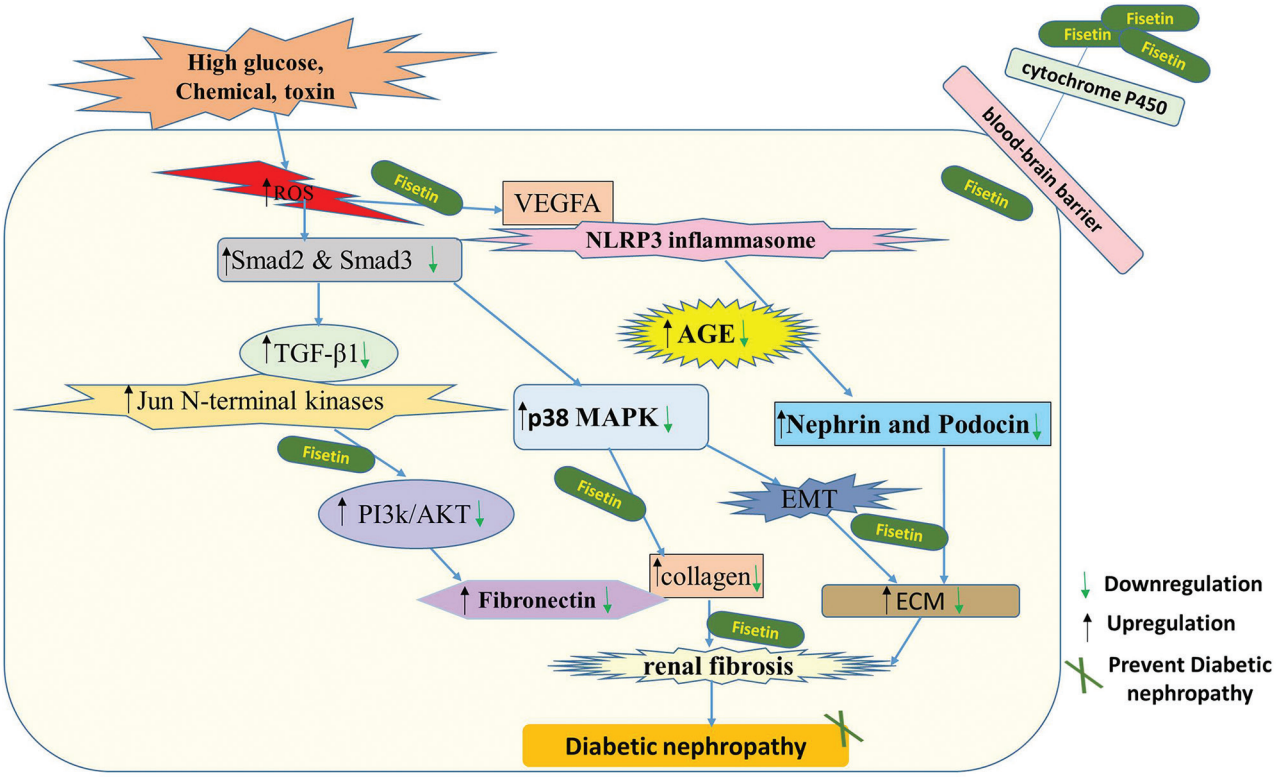

Figure 2. Mechanism of action of fisetin in the protection of diabetic nephropathy.
Abbreviations: VEGFA: Vascular endothelial growth factor A; ROS: Reactive oxygen species; NLRP3: NLR family pyrin domain containing 3; AGE: Advanced glycation end-product; MAPK: Mitogen-activated protein kinases; TGF-β1: Transforming growth factor-β1; EMT: Epithelial-to-mesenchymal transition; ECM: Extracellular matrix.

sepsis models by specifically inhibiting cyclooxygenase-2 (COX-2) and ameliorating liver damage in animal studies. Moreover, kaempferol decreased the excessive production of TNF-α, IL-1β, IL-6, ICAM-1, and VCAM-1 in LPS-treated groups. Kaempferol reduces COX-2 expression while simultaneously inhibiting the production of MCP-1, ICAM-1, and VCAM-1.[61] Oxidative stress is triggered by major signaling pathways, such as the MAPK signaling cascades. Activation of these proteins alters stress response pathways unique to particular cell types and conditions, causing apoptosis through phosphorylation of JNK and P38. As a biological mediator between oxidative stress and the pathogenic processes, ASK1 could be a potential therapeutic target to stop oxidative stress-related kidney damage. By blocking the ROS-mediated MAPK signaling pathway, kaempferol lessens drug-induced renal tubular damage.[62] The cytoplasm contains the inhibitory protein IκBα, while cisplatin-mediated ROS trigger signaling cascades involving p53, MAPK, and NF-κB. It has been demonstrated that phosphorylation of IκBα contributes to the activation of NF-κB, which translocates to the nucleus and activates inflammation-related genes, causing damage to renal cells. Kaempferol modulates NF-κB levels by preventing IκB kinase (IKK) phosphorylation and IκBα degradation, thereby reducing the risk of cisplatin-induced kidney damage.[63] According to Yuan *et al*., calcium oxalate (CaOx) crystal deposition and crystal-induced renal TEC injury are the main factors to the development of CaOx nephrolithiasis. Excess ROS generated during oxidative stress is regulated by NOX. Renal oxidative stress and inflammation have been associated with elevated NOX2 expression. The activation of the NOX isoenzyme suppresses the oxidative and inflammatory damage produced by the crystals, as well as the generation of adhesion molecules, by downregulating the NOX2 signaling pathway. Kaempferol may have a significant role in reducing the quantity of CaOx crystals that deposit in the renal cell.[64] Nevertheless, kaempferol treatment decreased production of proinflammatory cytokines such as TNF and MPO, which lessens leukocyte infiltration and kidney damage. In addition, kaempferol regulated NF-kB levels, inhibited the activation of the IKK, and reduced drug-induced renal inflammation.

3.7.4. Other bioactive compounds

Quercetin, a flavonol has been shown to protect DNA by lowering oxidative stress. In kidney damage caused by ionizing radiation, quercetin inhibits neutrophil infiltration and subsequent release of proinflammatory biomarkers, reducing oxidative stress-related DNA damage and apoptosis. Moreover, quercetin reduced oxidative stress, ROS, and thiobarbituric acid induced by lead exposure, preventing nephrotoxicity.[65] Similarly, quercetin's anti-apoptotic and antioxidant properties protect against kidney damage caused by titanium dioxide nanoparticles. In addition, quercetin treatment improved kidney function by increasing serum SOD and lactate dehydrogenase levels, and total antioxidant activity, demonstrating nephroprotective properties. This activity is believed to be caused by quercetin's ability to decrease the production of malondialdehyde and its capacity to remove ROS. Nrf2 and HO-1 are primarily activated by free radicals and ROS. The Nrf2/HO-1 pathway may be crucial for boosting the antioxidant moieties of glutathione (GSH), SOD, and GPx in relation to nephrotoxicity. In animals with copper sulfate-induced[66] and gentamicin-induced kidney damage, quercetin significantly increased the mRNA expression of HO-1 and Nrf2 when administered at a dose of 50 mg/kg.[67-69] The Food and Drug Administration has classified quercetin as "Generally Recognized as Safe" for use as a dietary supplement due to its well-established safety and tolerability profile in humans. Another study reported that myricetin is a bioactive phytocompound that has historically been used to treat a variety of ailments, including malaria, dysentery, diarrhea, and hypertension. Different parts of the plant, such as its fruits, bark, and leaves, have been utilized in these treatments. Other reported uses include antihypertensive and vasodilatory properties, analgesic and anti-inflammatory properties, antimalarial activity, and antidiabetic properties.[51] Flavonoids are potential substances to explore further for the development of innovative CKD therapy agents. However, the dearth of clinical studies implies that further research is required before flavonoids can be applied in medical treatments. Finding the metabolites produced after dosage and increasing bioavailability is also essential, as they could increase the advantages of flavonoids.[70] A flavone called luteolin, which is naturally present in various plants, has several pharmaceutical properties, like anti-inflammatory effects. It also lessens kidney damage caused by mercuric chloride. Luteolin decreases total TNF-α expression and several other indicators of inflammation by blocking NF-kB and activating the Nrf2 pathway.[71] In the Middle East, it has been used as traditional medicine since ancient times. The primary aglycones found are rhamnocitrin, kaempferol, quercetin, and rhamnetin. Renal colic and its associated symptoms were treated by the ancient Egyptians with a fruit decoction that also relieved prostatic pain, urolithiasis, and kidney inflammation. Raising urine pH and citrate concentration, reducing urine oxalates, and protecting renal epithelial cells from calcium oxalate monohydrate crystals have been shown to limit the oxalate formation associated with the formation of kidney stones.[72,73] Among the Lespedeza species, *Lespedeza*

capitata is less studied, although extracts from its leaves and stems, as well as the roots of *Asparagus racemosus* (family Asparagaceae), are used for urinary tract and KD due to the presence of bioactive compounds, including quercetin, apigenin, resveratrol, quercetin-3-D-galactoside, 3,3',4'-trihydroxyflavone (synonym 5,7-dideoxyquercetin), and 6-methyldihydroquercetin.[74-76]

3.8. Glucagon-like peptide 1 receptor agonists (GLP-1RAs)

The human GLP-1RAs are stimulated by the pharmaceutical class of peptides known as GLP-1RAs. There is debate regarding whether GLP-1RAs affect glomerular hemodynamics. GLP-1RAs may reduce glomerular hyperfiltration by reducing vasoconstriction induced by endothelin-1 and Angiotensin II. However, in theory, tubule-glomerular feedback would cause vasoconstriction of the pre-glomerular arteriole in response to reduced proximal salt reabsorption. However, the current study found that exenatide had a net vasodilatory impact on pre-glomerular arterioles, indicating a greater direct vasodilation effect. According to these results, GLP-1RAs are renal vasodilators and proximal diuretics that, in healthy individuals, have a negligible effect on tubule-glomerular feedback. It is probable that GLP-1 protects the renal system from damage caused by oxidation because GLP-1R activation stimulates the cyclic adenosine monophosphate–protein kinase A pathway, which results in antioxidative actions.[40] GLP-1RAs also decreased the expression of a number of inflammatory markers in rats in a diabetic nephropathy model, including collagen I, alpha-smooth muscle actin, tubulointerstitial TNF-alpha, MCP-1, fibronectin, and prevented tubulointerstitial lesions. These biomarkers have all been linked to diabetic nephropathy.[77]

4. Conclusion

Research on the prevention and protection of slow-progressing renal illnesses has been carried out globally. At present, dialysis and kidney transplantation are the primary treatments for KD, but these options are very expensive and have a number of drawbacks. In light of these challenges, further research is required to prevent and treat ESKD and to prolong the lives of KD patients. The current research on KD shows potential for opening new pathway to reduce the global burden of KD.

This review primarily highlights that ACEIs, ARBs, renin inhibitors, apoptosis-based treatment strategies, phytomedicines, JAK/STAT inhibition, and TNF inhibition may offer nephroprotective effects well beyond their main indications for diabetic nephropathy, kidney cancer, AKI, and CKD. Moreover, combining these therapies with a specific administration route could enhance their effectiveness, as they may provide additive nephroprotective effects. Future research focused on molecular pathway will be necessary to determine the effect of these treatments.

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Conflict of interest

The authors declare that they have no competing interests.

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