ДОСЛІДЖЕННЯ

Research

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Pharmacotherapeutic Advances in Protecting Renal Function: Emerging Drug Strategies for Kidney Disease Management

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Abstract

Chronic kidney disease (CKD) is a progressive condition associated with substantial morbidity, mortality, and healthcare burden worldwide. Although the traditional renoprotective treatment methods, including renin-angiotensin-aldosterone system blockage and glycemic regulation, have been used long ago, a substantial number of patients still report progressive deterioration of kidney function. The pharmacotherapy over the last few years has transformed how kidney disease should be treated with new drug classes with novel approaches towards alternative and understudied pathogenic pathways. This is a holistic narrative literature review that combines the existing information on proven and novel pharmacotherapeutic methods to guard against renal dysfunction. Such innovative agents as sodium-glucose cotransporter-2 inhibitors, non-steroidal mineralocortin receptor antagonists, endothelin receptor antagonists, anti-inflammatory and anti-fibrotic agents have become available, and each of them targets hemodynamic, metabolic, inflammatory, and fibrotic pathways of renal injury. Also, the recent developments of precision pharmacotherapy, such as targeted biologics, RNA-based therapeutic options, and pharmacogenomics, also point to the individualised approach to treatment. In the review, clinical issues concerning the safety of drugs, translation gaps, and their real-world practice are also mentioned. Altogether, the available pharmacotherapeutic approaches can be of rich potential to reduce the CKD progression rate and enhance renal outcomes in the long term, which could contribute to a paradigm shift in favour of multi-pathway and individual renoprotective therapy.

Keywords: Chronic kidney disease; Renoprotection; Pharmacotherapy; Emerging renal therapies; Precision nephrology

1. Introduction

Chronic kidney disease (CKD) is a significant and increasing worldwide societal health issue, with a prevalence of about 10-13% in the adult population and a significant amount of morbidity, mortality, and health care spending [1]. According to the Global Burden of Disease (GBD) research, CKD is ranked among the most rapidly escalating causes of Years of Life Lost due to the ageing of the population, rising rates of diabetes mellitus, hypertension, and cardiovascular disease [1]. On top of its direct effects on renal health, CKD leads to the development of a high risk of cardiovascular events, infections, and premature death, which explains why

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effective strategies to maintain renal function and slow the progression of the disease should be developed.

The loss of renal functionality in CKD is normally progressive and irreversible and is caused by a complicated interplay of hemodynamic, inflammatory, metabolic, and fibrotic pathways [2]. Kidney diseases in their initial stages are often asymptomatic, failing to diagnose and take advantage of the situation. Pathophysiologically, prolonged hypertension of the glomeruli, maladaptive hyperfiltration, tubular necrosis and necrosis of interstitial fibrosis are involved in the progressive loss of functional kidney cells, which eventually leads to end-stage renal disease (ESRD) that necessitates either dialysis or kidney transplantation [3]. Notably, the speed of the deterioration of renal functions differs across individuals, and it is determined by the underlying aetiology, comorbid conditions, genetic predisposition, and therapeutic interventions.

Over a number of decades, the traditional renal protective interventions have mainly prioritised blood pressure management and renin-angiotensin-aldosterone system (RAAS) inhibition. Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) have been proven to be effective in slowing the progression of CKD, especially in proteinuric kidney disease, through intraglomerular pressure and proteinuria reduction [4]. The clinical trials that were conducted formed the cornerstone of CKD management, having RAAS blockade as the foundation of the international clinical practice guidelines [2]. Nonetheless, the advantages notwithstanding, RAAS inhibitors cannot completely prevent the renal decline of functions, and a significant percentage of patients still develop advanced CKD.

Further, traditional treatments have drawbacks due to a lack of full activity and the presence of side effects such as hyperkalemia, hypotension, and acute changes in the glomerular filtration rate, especially in patients with severe diseases or multimorbidity [2]. Combination therapy to intensify RAAS blockade has not shown any significant renal benefit and has been linked to a greater amount of harm. These shortcomings have unveiled important gaps in current treatment paradigms and affirmed the necessity of new pharmacological interventions that address other pathophysiology processes in kidney disease progression.

Over the past few years, the field of renal protection has undergone considerable changes due to the development of potent pharmacotherapy. New classes of drugs, originally specified to have metabolic or cardiovascular effects, have proven to be strong renoprotective regardless of their main actions. Sodium12-glucose co-transporter-2 (SGLT2) inhibitors are among those that have demonstrated unparalleled performance in CKD disease progression, albuminuria, and decreased kidney failure risks in varied patient groups, including non-diabetic patients [5]. The evidence of large randomised controlled trials supports the idea that SGLT2 inhibitors can slow the rate of the estimated glomerular filtration rate (eGFR) decrease and improve the renal outcomes, whether used in conjunction with standard-of-care therapy.

In addition to the SGLT2 inhibitors, non-steroidal mineralocortin receptor blocking agents, endothelin receptor blocking agents, anti-inflammatory agents, and new metabolic regulators, the therapeutic agents for the protection of renal concerns are increasing. These agents work on major pathways, including inflammation, fibrosis, oxidative stress, and dysfunction of the endothelium, to provide a complementary mechanism to conventional hemodynamic therapies. Together, these developments are an indication of a paradigm shift, whereby the unidirectional intervention strategy has been replaced by a mechanism-directed approach to kidney disease management.

This comprehensive review aims to critically examine current and emerging pharmacotherapeutic strategies for protecting renal function in kidney disease. By synthesising evidence from clinical trials, mechanistic studies, and recent guidelines, this review seeks to provide an integrated overview of established and novel drug therapies, highlight their mechanisms of action, clinical efficacy, and safety considerations, and discuss future directions in pharmacological renoprotection. Through this approach, the review aims to inform clinical practice and support the development of more effective, personalised treatment strategies for patients with kidney disease.

2. Methodology

A comprehensive narrative review of the literature was conducted to identify and synthesise current evidence on pharmacotherapeutic strategies aimed at protecting renal function in kidney disease. Electronic database searches were performed using PubMed, Scopus, Web of Science, and Google Scholar to capture a broad range of clinical, translational, and pharmacological studies relevant to renoprotection.

The literature search included articles published between January 2010 and March 2025, ensuring inclusion of both foundational studies and recent advances. Search terms were selected to reflect key concepts related to renal protection and pharmacotherapy and included combinations of the following keywords: *"chronic kidney disease," "renal protection," "pharmacotherapy," "renoprotective agents," "emerging renal therapies," "SGLT2 inhibitors," "mineralocorticoid receptor antagonists,"* and *"anti-fibrotic drugs."* Boolean operators (AND, OR) were applied to refine search results.

Inclusion criteria involved publications that were peer-reviewed articles in English that included randomised controlled trials, observational studies, meta-analyses, and high-quality review articles evaluating the effect of pharmacological interventions with proven or possible renoprotective effects. Case reports, conference abstracts, editorials, and non-peer-reviewed literature were not looked at. To increase completeness, the reference lists of the concerned articles were manually filtered in a bid to find more relevant studies.

The formal risk-of-bias assessment was not conducted since this was a narrative review. Rather, the focus was on studies that had a high level of methodological design, a large sample size, and clinically significant renal outcomes. Data were reviewed qualitatively, and the

emphasis was given to the mechanisms of action, therapeutic efficacy, safety profiles, and new trends in pharmacological renoprotection.

Ethical approval was not required for this study, as it was based exclusively on the analysis of previously published, publicly available literature.

3. Pathophysiological Basis of Pharmacological Renoprotection

Chronic kidney disease development is influenced by a complicated interconnection between hemodynamic, inflammatory, metabolic and oxidative processes that, together, stimulate nephron loss and irreversible structural changes. The objective of pharmacological renoprotection is to break these maladaptive processes, to conserve the remaining renal functions, and to slow the further development of end-stage renal diseases. The pathophysiology is a complex field, and it is difficult to appreciate the therapeutic rationale behind the established and emerging drug strategies without an understanding of the underlying pathophysiology.

3.1 Hemodynamic and Glomerular Mechanisms

3.1.1 Intraglomerular Hypertension

Sustained intraglomerular hypertension is one of the first and most important causes of renal injury in CKD. The resulting loss of functional nephrons causes compensatory hyperfiltration in the nephrons which remain, which causes the glomerular capillary pressure to rise and imposes increased mechanical pressure on the glomerular filtration barrier [6]. Although hyperfiltration is initially adaptive, chronic hyperfiltration increases podocyte injury, mesangial proliferation and glomerulosclerosis. Such effects of structural alteration impair the selectivity of filtration, resulting in proteinuria that itself is a mediator of additional tubular and interstitial injury.

The renoprotective strategies have thus revolved around pharmacological interventions that lower intraglomerular pressure. The agents which control afferent and efferent arteriolar tone can suppress hyperfiltration and mechanical damage. Recently, medications like the SGLT2 inhibitors have proved to be able to restore the tubuloglomerular feedback, therefore, reducing the intraglomerular pressure despite the reduction of systemic blood pressure [7]. This process has come to light as one of the major agents in their renoprotective action.

3.1.2 Renin-Angiotensin-Aldosterone System Activation

Persistent renin-angiotensin-aldosterone system (RAAS) activation is the main cause of hemodynamic stress and facilitation of progressive renal injury. The Angiotensin II narrows the efferent arteriole, which elevates the glomerular pressure, and also has pro-inflammatory, pro-fibrotic, and pro-oxidative effects on renal cells [6]. Aldosterone also adds to the damage of the renal tissue by increasing sodium retention, endothelial dysfunction, and fibrosis.

RAAS hyperactivity is especially high in proteinuric kidney disease and diabetic nephropathy, in which it exaggerates hemodynamic and non-hemodynamic injury mechanisms. Pharmacological RAAS inhibition has a moderating effect on these effects, lowering intraglomerular pressure, proteinuria, and downstream inflammatory and fibrotic signalling cascades. Nevertheless, partial blockage of RAAS activity and compensatory processes restrict the long-term efficacy of traditional RAAS blockade, which requires complementary disease treatment using adjunctive therapies.

3.2 Inflammatory and Fibrotic Pathways

3.2.1 Cytokine-Mediated Injury

Inflammation plays a key role as an intermediary of progressive renal injury in a variety of CKD etiologies. Renal damage results in the promotion of innate and adaptive immune responses, the production of more pro-inflammatory cytokines, chemokines, and adhesion molecules [8]. These cytokines facilitate the infiltration of leukocytes into the renal interstitium, enhance the damage of tubules and increase the local inflammatory response.

Some of the cytokines that have been implicated in the pathogenesis of CKD are tumour necrosis factor-alpha (TNF-alpha), interleukin-6 (IL-6) and transforming growth factor-beta (TGF-beta). The constant cytokine signalling disturbs the normal cellular repair mechanisms and promotes maladaptive remodelling. Pathways of the inflammatory process combine with hemodynamic stress and metabolic dysregulation, developing into a vicious cycle of injury. Anti-inflammatory pharmacological agents have thus become the possible renoprotective therapies, which are meant to reduce the immune-mediated harmful effects and maintain the renal architecture.

3.2.2 Progression to Renal Fibrosis

Renal fibrosis is the last typical process of CKD, which involves an overgrowth of extracellular matrix, tubular atrophy, and functional tissue irreversible loss [9]. The prolonged response to inflammation, fibroblast and myofibroblast activation, and TGF-β sustained signalling activate fibrogenesis. Fibrosis increases to the point that the renal tissue is no longer able to regenerate, resulting in a further decrease in glomerular filtration rate.

Targeting fibrotic pathways has become a major focus of emerging pharmacotherapeutic strategies. Mineralocorticoid receptor, TGF-β, downstream profibrotic mediator, and other drug classes that repress activations of these pathways have shown potential benefits in fibrosis inhibition and renal function deterioration. Notably, anti-fibrotic treatment could be used to supplement hemodynamic measures with the purpose of overcoming structural injury that cannot be entirely reversed by blood pressure therapy.

3.3 Metabolic and Oxidative Stress Pathways

3.3.1 Mitochondrial Dysfunction

Metabolic dysregulation and mitochondrial dysfunction play increasingly recognised roles in CKD progression. Renal tubular cells require plenty of energy, and the deterioration of mitochondrial oxidative phosphorylation decreases the production of ATP, raises

the occurrence of reactive oxygen species (ROS) formation and enhances cell vulnerability to damage [10]. Mitochondrial dysfunction also facilitates apoptosis and inhibition of the cellular repair process, which increases the loss of nephrons.

Pharmacological agents that improve mitochondrial efficiency or reduce oxidative stress have demonstrated renoprotective potential in experimental and clinical studies. Control over cellular metabolism, especially the pathways that affect glucose processing and the oxidation of fatty acids, has become a new therapeutic target. These processes can be one of the reasons for renal advantages with some metabolic agents, other than their systemic consequences.

3.3.2 Endothelial Injury

Endothelial dysfunction is a significant pathogen of CKD progression and cardiovascular comorbidity. This is caused by oxidative stress, inflammation and activation of RAAS, resulting in impaired endothelial nitric oxide synthesis and vasoconstriction, decreased perfusion and microvascular rarefaction in the kidney [11]. Endothelial damage intensifies ischemia, facilitates inflammation and further interferes with glomerular and tubular activity.

The pharmacological approaches capable of restoring the endothelial activity, decreasing oxidative stress, or increasing the bioavailability of nitric oxide might thus possess renoprotective effects. Such therapies target a more fundamental pathophysiology of renal disease, which has not been well considered in the past in the treatment of CKD, by enhancing microvascular health and tissue oxygenation. These are the key hemodynamic, inflammatory, metabolic, and fibrotic mechanisms leading to renal dysfunction, as well as the pharmacological targets, and they are summarised in Figure 1.

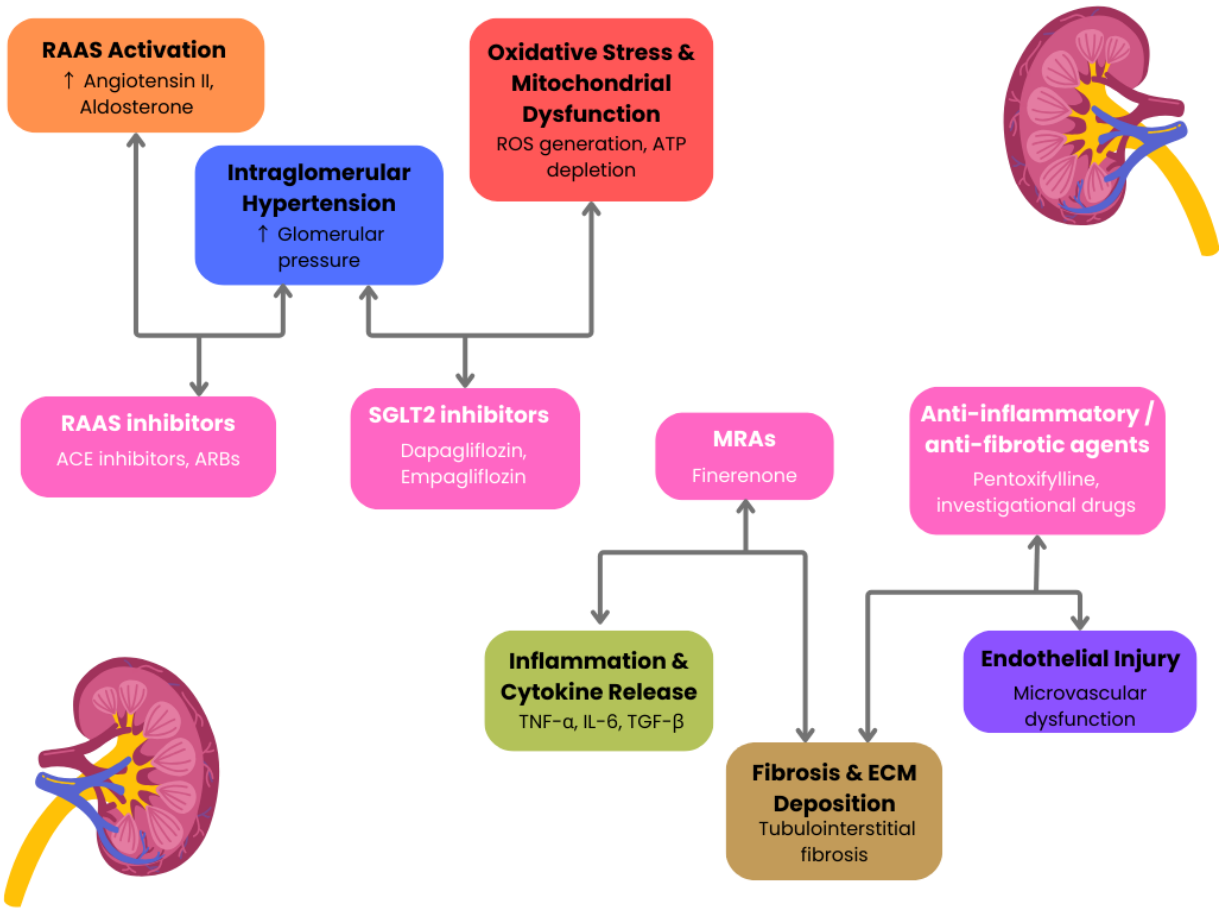

Fig 1. Pathophysiological Pathways Driving Renal Function Decline and Targets of Pharmacological Renoprotection

4. Established Pharmacotherapies for Renal Protection

Pharmacological strategies aimed at preserving renal function have historically focused on modulating hemodynamic stress and metabolic dysregulation, two central drivers of chronic kidney disease progression. The renoprotective therapy has been based on inhibition of the renin-angiotensin-aldosterone system (RAAS) and optimisation of glycemic control, among others. These old classes of drugs are still the basis of kidney disease therapy, even though new classes have been introduced in the recent past.

4.1 Renin-Angiotensin-Aldosterone System (RAAS) Inhibitors

4.1.1 Angiotensin-Converting Enzyme Inhibitors

Angiotensin-converting enzyme inhibitors (ACE inhibitors) were the initial pharmacological interventions to exhibit certain renoprotective effects in addition to reducing blood pressure at a systemic level.

ACE inhibitors prevent the conversion of angiotensin I into angiotensin II and inhibit the efferent arteriolar vasoconstriction, which lowers the intraglomerular pressure and decreases proteinuria. Such hemodynamic effects are translated into a slower rate of renal dysfunction, especially in patients with proteinuric kidney disease [12].

According to seminal clinical trials, ACE inhibitors have a significant effect in reducing the risk of doubling serum creatinine and the development of end-stage renal disease, particularly in diabetic nephropathy. The renoprotective effects of ACE inhibition are directly related to the decrease in albuminuria as a marker and mediator of kidney disease progression. As a result, ACE inhibitors are currently being used as the first-line agents in patients with CKD and albuminuria, irrespective of diabetic status.

4.1.2 Angiotensin Receptor Blockers

Angiotensin receptor blockers (ARBs) provide another method of RAAS inhibition as they preferentially block the angiotensin II type 1 receptor. This has several of the same hemodynamic and anti-proteinuric effects as the ACE inhibitors without the side effects of bradykinin-mediated mechanisms (cough, angioedema). The renoprotective effect of ARBs in diabetic and non-diabetic CKD patients has been proven by large randomised controlled trials [13].

ARBs have shown impressive proteinuria reduction and reduced estimated glomerular filtration rate progression, having solidified their place as a primary treatment in CKD. ACE inhibitors and ARBs are therapeutically equivalent regarding protecting against renal disease, and the choice is subject to patient-related and tolerability factors in clinical practice.

4.1.3 Evidence, Benefits, and Limitations

Despite their proven benefits, RAAS inhibitors have notable limitations. Even in patients receiving optimal residual renal protection despite receiving the best RAAS blockade, a significant number of patients report residual renal risk with these agents, demonstrating the incomplete protection of these agents. Furthermore, the RAAS inhibition can be linked to such negative outcomes as hyperkalemia, hypotension, and an acute decrease in glomerular filtration rate, especially in end-stage CKD or in a volume-depleted situation [14]. Notably, dual RAAS blockade, ACE and ARBs use has not shown an add-on effect on renoprotection and has been linked to greater adverse events, such as acute kidney injury. Such discoveries have placed the necessity to adopt complementary pathogenic therapy adjunctive methods that do not worsen the situation of hemodynamic instability.

4.2 Conventional Glycemic Control Agents with Renal Benefits

4.2.1 Metformin

Metformin has been the primary pharmacological agent in the management of type 2 diabetes mellitus for a long ago and has shown significant renal advantages beyond glucose regulation. Metformin indirectly ameliorates the renal injury caused by hyperglycemia by enhancing insulin sensitivity and decreasing hepatic gluconeogenesis. It is indicated by observational and clinical studies that the use of metformin is linked to less rapid development of diabetic kidney disease and lower mortality rates in patients with mild-to-moderate CKD [15].

In the past, the issue of lactic acidosis has been a cause of restricting the use of metformin in patients with poor renal function. There is, however, a growing amount of evidence that has prompted updated recommendations that it may be safely used in patients with moderate CKD with necessary dose modifications and monitoring. The positive physiological cardiovascular and metabolic profile of metformin also supports its use in renoprotective measures towards diabetic patients.

4.2.2 Glucagon-Like Peptide-1 Receptor Agonists

Glucagon-like peptide-1 (GLP-1) receptor agonists represent another class of glucose-lowering agents with demonstrated renal benefits. These medications enhance glycemic regulation by enhancing glucose-dependent insulin release, as well as inducing weight loss, a decrease in blood pressure and anti-inflammatory activity. Consistent results in large cardiovascular outcome studies demonstrated that GLP-1 receptor agonists lower albuminuria and delay the process of diabetic kidney disease [16].

Renoprotective action of GLP-1 receptor agonists seems to be achieved by indirect metabolic and direct renal mechanisms that include reduction of oxidative stress and renal inflammation. Although their effect on hard renal outcomes like the development of end-stage renal disease is not as high as that of SGLT2 inhibitors, GLP-1 receptor agonists offer some significant additive effects, especially in patients with type 2 diabetes and with high cardiovascular risk. Table 1 provides a summary of already known pharmacotherapies, their action, renal advantages and clinical constraints.

Table 1. Established Pharmacotherapies for Renal Protection: Mechanisms, Benefits, and Limitations

Drug Class	Representative Agents	Primary Mechanism of Action	Renal Benefits	Key Limitations
ACE inhibitors	Enalapril, Captopril, Lisinopril	Inhibition of angiotensin II formation; efferent arteriolar dilation	↓ Intraglomerular pressure, ↓ proteinuria; slowed CKD progression	Hyperkalemia; hypotension; acute eGFR decline
Angiotensin receptor blockers (ARBs)	Losartan, Irbesartan, Valsartan	Blockade of angiotensin II type 1 receptor	Reduced proteinuria; renoprotection in diabetic and non-diabetic CKD	Hyperkalemia; limited efficacy as monotherapy

Biguanides	Metformin	Improved insulin sensitivity; reduced hepatic gluconeogenesis	Slower diabetic CKD progression; cardiovascular benefit	Contraindicated in advanced CKD; lactic acidosis risk
GLP-1 receptor agonists	Liraglutide, Semaglutide	Enhanced insulin secretion; weight loss; anti-inflammatory effects	Reduced albuminuria; slowed diabetic kidney disease	Gastrointestinal effects; injectable formulations

Altogether, RAAS inhibitors and traditional glycemic control agents have provided the groundwork of pharmacological renal protection. Although these treatments have helped to achieve significant progress in improving the condition of patients with CKD, their limitations have made it important to have newer classes of drugs, which address other mechanisms of kidney injury. Combining the old and new therapies would be a monumental move towards holistic and personalised renoprotective therapy.

5. Emerging Pharmacotherapeutic Strategies in Renal Protection

The shortcomings of the traditional reneoprotective medication have led to the production of new pharmacological compounds that address complementary and heretofore underutilized renal disease disease-progression pathways. Over the past few years, a number of new drugs classes have exhibited significant effectiveness in slowing the rate of renal failure, decreasing albuminuria, and improving long-run renal outcomes in a variety of patients. These innovations signify the paradigm shift in the treatment of chronic kidney disease, which is the transition to hemodynamic control to multi-pathway intervention.

5.1 Sodium–Glucose Cotransporter-2 (SGLT2) Inhibitors

5.1.1 Renal Mechanisms Beyond Glucose Lowering

The SGLT2 inhibitors were first applied as glucose-lowering medications in type 2 diabetes mellitus but have since become one of the most important pharmacologic advances in kidney protection. Their renoprotective effects are far much greater than those in the glycemic control and they are seen in diabetic and non-diabetic CKD populations. On a renal level, SGLT2 inhibition decreases proximal tubular sodium and glucose uptake, which causes an increase in the sodium supplied to the macula densa and reestablishes tubuloglomerular feedback [17].The effect of this mechanism is the afferent arteriolar vasoconstriction, decreased intraglomerular pressure, and suppression of hyperfiltration-major contributors of progressive nephron damage. Besides hemodynamic effect, SGLT2 inhibitors have anti-inflammatory, anti-oxidative, and anti-fibrotic effects, mitochondrial efficiency, and renal hypoxia. All these pleiotropic effects lead to long-term renal functional preservation and less structural damage.

5.1.2 Major Clinical Trial Evidence

Robust evidence supporting the renoprotective efficacy of SGLT2 inhibitors has emerged from multiple large randomized controlled trials. These studies have proven that the risk of CKD development is invariably reduced, estimated glomerular filtration rate levels remain low, and the disease advances to the end-stage renal disease. Notably, the benefits have been witnessed on a broad range of baseline renal functioning and regardless of having diabetes or not [18].The uniformity of renal benefit trials has promoted a fast introduction of SGLT2 inhibitors in global CKD therapy prescribing. Their positive safety, cardiovascular and renal safety, make SGLT2 inhibitors the mainstay of therapy of current nephrology. Current research is in progress to determine their use in more advanced CKD and in combination with other renoprotective agents.

5.2 Non-Steroidal Mineralocorticoid Receptor Antagonists

Mineralocorticoid receptor hyperactivation is essential in stimulating inflammation, oxidative stress and fibrosis in chronic kidney disease. Although the use of the traditional steroidal mineralocortisoid receptor antagonists like spironolactone which have shown renoprotective effects has been restricted due to side effects specifically hyperkalemia and endocrine disturbances.

Finerenone, a non-steroidal mineralocorticoid receptor antagonist is a new generation of the targeted therapy; it inhibits mineralocorticoid receptor-mediated pathogenic signaling selectively, with a low number of off-target effects. Fenereno is more receptor selective and tissue-distributed, unlike its predecessors, which allows it to demonstrate better anti-inflammatory and anti-fibrotic effects with better tolerance [19].

Clinical trials of large scale have shown that finerenone is very effective in reducing albuminuria, delaying the progression of eGFR, and reducing the prevalence of kidney failure as a response to diabetic kidney disease when used in combination with optimized RAAS blockade. These results demonstrate the relevance of non-hemodynamic pathways as the target of CKD. Continued studies are underway on the next generation of mineralocorticoids receptor antagonists that are more renal specific and have fewer electrolyte disrupting effects. Major new pharmacotherapeutic agents and clinical trial evidence are highlighted in Table 2.

Table 2. Emerging Pharmacotherapeutic Agents and Key Clinical Evidence for Renal Protection

Drug Class	Key Agent(s)	Targeted Pathway	Major Clinical Trial(s)	Principal Renal Outcome
SGLT2 inhibitors	Dapagliflozin, Empagliflozin	Tubuloglomerular feedback restoration; reduced hyperfiltration	DAPA-CKD; EMPA-KIDNEY	Slower eGFR decline; ↓ risk of kidney failure

Non-steroidal MRAs	Finerenone	Anti-inflammatory and anti-fibrotic MR signalling	FIDELIO-DKD; FIGARO-DKD	Reduced albuminuria; delayed CKD progression
Endothelin receptor antagonists	Atrasentan	Selective endothelin-A receptor blockade	SONAR	Reduced proteinuria; renal injury attenuation
Anti-inflammatory agents	Pentoxifylline	Cytokine (TNF-α) suppression; anti-oxidative effects	Multiple adjunctive CKD trials	Reduced proteinuria; modest eGFR preservation

5.3 Endothelin Receptor Antagonists

The endothelin system is a strong constitutive to vascular tone, inflammation and fibrosis, and its hyper- or hypo-regulation has been strongly implicated in the progression of CKD. Endothelin-1 facilitates vasoconstriction, podocyte injury, proteinuria, and fibrotic remodelling, so it is an appealing drug target. The first-generation endothelin receptor antagonists showed renoprotective properties but were constrained by side effects, including retention of fluid and heart failure.

The recent approaches have been concerned with the design of selective endothelin A receptor antagonists to optimise the benefits of the kidneys and limit systemic toxicity. A reduction in albuminuria and a decrease in renal injury have been demonstrated to be promising with these agents in well-selected patient populations [20]. Importantly, combination strategies integrating endothelin receptor antagonists with RAAS inhibitors or SGLT2 inhibitors are being actively investigated to enhance efficacy while mitigating adverse effects.

Selective endothelin blockade is an interesting adjunctive treatment method, although not currently actively used in clinical practice, in patients with high residual renal risk. The continuous clinical trials will help to determine their safety profile and place in the combination renoprotective regimens in the long term.

5.4 Anti-Inflammatory and Anti-Fibrotic Agents

5.4.1 Pentoxifylline

Pentoxifylline, a non-selective phosphodiesterase inhibitor with anti-inflammatory properties, has gained attention as a potential renoprotective agent. Its effects of action encompass inhibition of pro-inflammatory cytokines like tumour necrosis factor-alpha, as well as the antioxidant response. The clinical research has shown that pentoxifylline helps to decrease proteinuria and also slows down the renal failure when combined with standard treatment in patients with CKD [21].

Pentoxifylline's favourable safety profile and low cost make it an attractive option, particularly in resource-limited settings. Nonetheless, inconsistent acceptability in trial design and patient populations has prevented widespread adoption, and additional large-scale researches are required to determine its best usage in CKD treatment.

5.4.2 Lessons from Failed and Ongoing Trials

Despite substantial progress, not all emerging renoprotective therapies have been successful. Several agents targeting fibrotic or metabolic pathways have failed to demonstrate sustained renal benefit or have been associated with unacceptable adverse effects. These outcomes underscore the complexity of CKD pathophysiology and the challenges of translating mechanistic promise into clinical efficacy.

Notably, the design of studies that are currently underway has taken lessons learned in failed trials to focus on patient selection, combination therapy, and clinically meaningful renal endpoints. The recent stream of anti-fibrotic and anti-inflammatory drugs is connected with a deeper comprehension of the heterogeneity of diseases and the necessity of individual treatment. Figure 2 shows the complementary processes by which the emerging pharmacotherapeutic agents have renoprotective actions in addition to the traditional hemodynamic regulation.

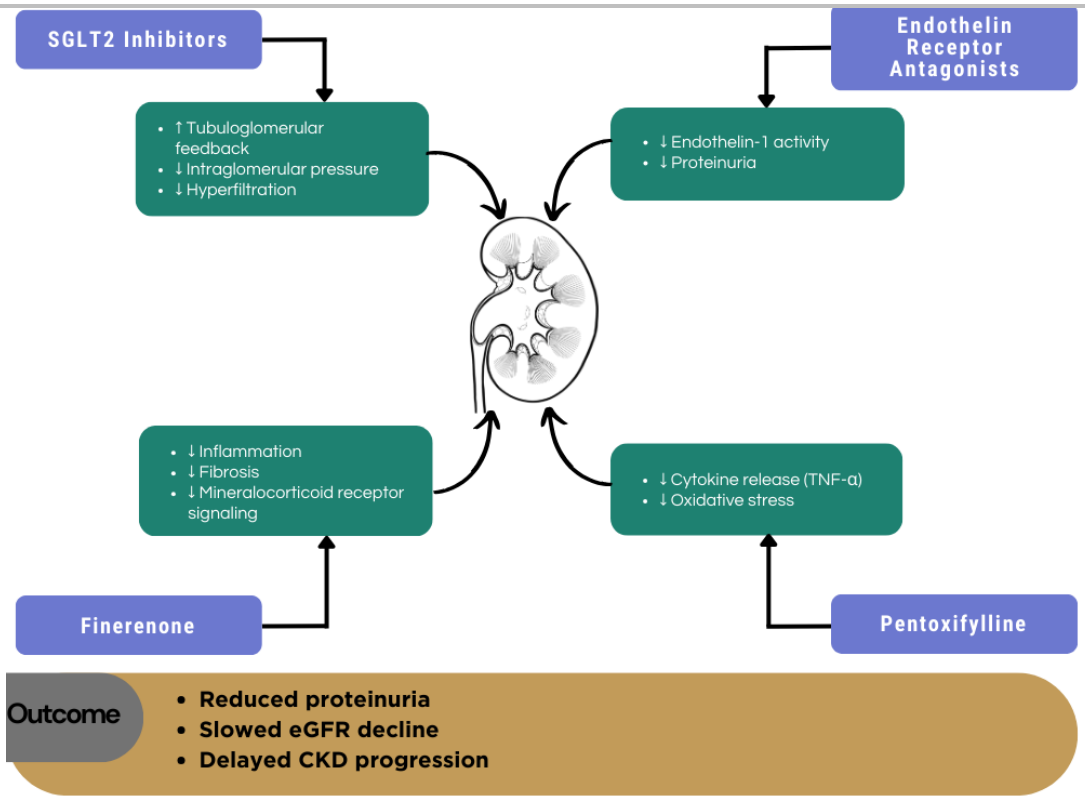

Fig 2. Mechanisms of Renal Protection Conferred by Emerging Pharmacotherapeutic Agents

6. Precision Pharmacotherapy and Novel Therapeutic Frontiers

Advances in molecular biology, genomics, and drug development have accelerated the transition toward precision pharmacotherapy in chronic kidney disease. Contrary to the traditional methods of one-size-fits-all treatment, precision medicine is supposed to focus on personalising an approach to treatment according to individual biological parameters, disease pathophysiology, and expected response to treatment. This paradigm is especially promising in the context of nephrology since the etiologies of CKD, its progression, and treatment outcomes are heterogeneous.

6.1 Targeted Biologic Therapies

Specific biologic therapies are a quickly developing novel development in the history of renal pharmacotherapy and are meant to precisely alter a set of molecular pathways involved in the progression of kidney diseases. Recombinant proteins and monoclonal antibodies have been engineered to attack cytokines, growth factors, and growth triggers to stimulate inflammation and fibrosis. Direct interference with pathogenic signalling cascades may enable biologic agents with a capability to provide the highly specific renoprotection with minimal off-target toxicity [22].

Inflammatory mediators, including tumour necrosis factor-α, interleukins and transforming growth factor-β, have been shown to possess renoprotective activity in preclinical models using several biologic therapies. In spite of the fact that clinical translation has proven tricky because of immunogenicity and safety issues, more recent developments in the field of antibody engineering and dosing regimens have led to renewed attention on biologic therapy of CKD. These treatments can be especially useful in immune-mediated renal diseases and subgroups of patients with an increased level of inflammation.

6.2 RNA-Based and Gene-Modulating Drugs

RNA-based therapeutics (antisense oligonucleotides, or ASOs, small interfering RNA, or siRNA, and microRNA modulators) have become an effective gene-regulating tool. These agents allow the selective suppression or promotion of the disease-relevant expression of genes, providing greater specificity than ever before in targeting renal pathogenic pathways [23]. RNA-based therapies have been considered in CKD to regulate fibrotic pathways, inflammatory cytokines, and metabolic controllers in nephron damage.

It is important to note that siRNA therapies of hepatic and renal pathways have already been granted regulatory approval elsewhere in disease domains, indicating the clinical viability of the method. The active nephrology approach involves gene-modulating techniques involving fibrosis-related genes and lipid metabolism pathways. Although there are still issues of delivery, stability, and off-target effects, nanoparticle-based delivery systems have changed by enabling renal targeting and improving therapeutic potential tremendously [24].

6.3 Pharmacogenomics and Individualised Treatment Strategies

Pharmacogenomics aims to enhance drug choice and dosing depending on genetic variation that affects drug metabolism, drug efficacy, and drug toxicity. The individual variability in the response to renoprotective therapy is also significant in CKD, which justifies the importance of individualised treatment plans.

Polymorphisms in genetic RAAS signalling, drug transporters, and metabolic enzymes have been indicated to alter the response to the drug therapy and the risk of adverse events [25].

Emerging evidence suggests that integrating genetic data with clinical and biochemical markers can improve the prediction of treatment response and renal outcomes. As one example, hereditary variations related to accelerated CKD can identify a patient who would benefit more from prompt intensive pharmacotherapy. In the same manner, the pharmacogenomic profiling could be used to reduce adverse drug reactions in high-risk populations, including patients with CKD at higher stages or multiple comorbidities.

Beyond genomics, multi-omics approaches incorporating transcriptomic, proteomic, and metabolomic data are being explored to refine patient stratification and therapeutic targeting. These initiatives are in line with the overall trend of moving towards precision nephrology, whereby treatment choices are informed by a combined appreciation of disease biology and not merely by clinical staging [26].

With the combination of accuracy in pharmacotherapy and new therapeutic horizons, there is transformative potential in renal protection. Although a lot of these approaches are still investigational, their evolution is an indication of a paradigm shift in the way kidney disease is treated on a personalised approach, as well as basing the treatment on mechanisms. With the ongoing improvement in both technological and analytical capabilities, the future of CKD management may be redesigned with the use of biologics, RNA-based therapies, and pharmacogenomics. Figure 3 illustrates the shift towards a more focused approach of pharmacotherapy, a renoprotective approach, and data-driven drug development.

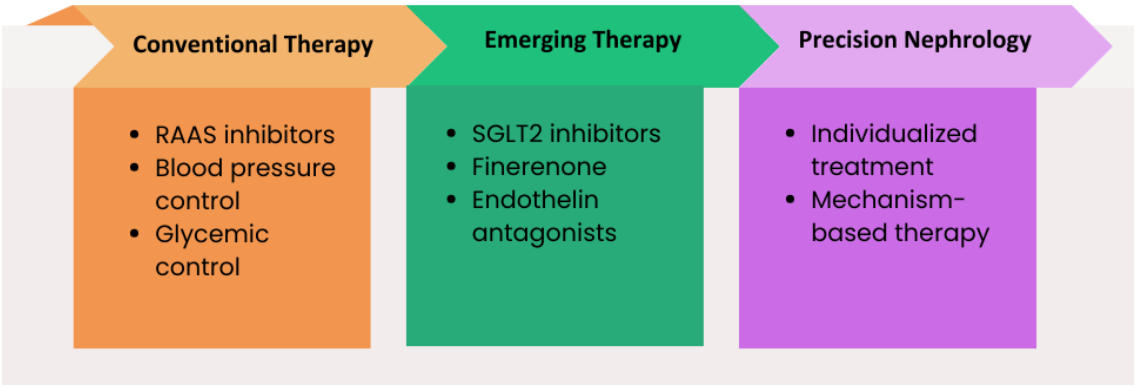

Fig 3. Evolution Toward Precision Pharmacotherapy in Chronic Kidney Disease

7. Clinical Challenges, Safety Considerations, and Future Perspectives

Although major breakthroughs have been achieved in pharmacotherapy to protect the kidneys, there are still a number of clinical issues that hinder the effective implementation of new treatment methods into practice. The tolerance of safety, gaps in the evidence, and the barriers to implementation are critical issues to be addressed to ensure patients with chronic kidney disease (CKD) receive the maximum benefit and the smallest harm.

7.1 Drug Safety and Renal Risk Mitigation

7.1.1 Nephrotoxicity

A variety of pharmacological drugs administered in CKD is associated with a predisposed risk of nephrotoxicity, especially in patients with a progressive disease, unstable renal dysfunction or comorbidities. Acute decreases of glomerular filtration rate, electrolyte imbalances and drug-related nephritis of interstitial nature are also of clinical interest. Even such drugs that have demonstrated renoprotective properties may bring about temporary decreases in estimated glomerular filtration rate, and this should be interpreted with care and monitored during drug initiation and dose progression [27].

7.1.2 Drug–Drug Interactions

Polypharmacy among CKD patients is not new, and it contributes significantly to drug-drug interactions. The use of renin-angiotensin-aldosterone system inhibitors, diuretics, nonsteroidal anti-inflammatory drugs, and, more recently, SGLT2 inhibitors can predispose patients to hypotension, hyperkalemia or AKI. Complete medication reconciliation and sensitivity to pharmacokinetic alterations related to the decreased renal clearance are the essential aspects of safe prescribing methods [28].

7.1.3 Monitoring Strategies

Effective renal risk mitigation requires structured monitoring strategies tailored to individual patient risk profiles. Renoprotective therapy should be started or escalated with regular evaluation of renal functions, serum electrolyte, and albuminuria levels. New digital health technologies and remote monitoring solutions could be used to identify poor outcomes earlier and make timely therapeutic changes, especially in the cases of high-risk groups.

Safety considerations, common adverse effects, and recommended monitoring strategies for renoprotective therapies are outlined in Table 3.

Table 3. Safety Considerations and Monitoring Strategies for Renoprotective Pharmacotherapies

Drug Class	Common Adverse Effects	Monitoring Parameters	Risk Mitigation Strategies
RAAS inhibitors	Hyperkalemia; hypotension; AKI	Serum creatinine; potassium; blood pressure	Gradual dose titration; electrolyte monitoring
SGLT2 inhibitors	Initial eGFR dip; volume depletion	Renal function; volume status	Patient education; temporary drug withholding
MRAs (Finerenone)	Hyperkalemia	Potassium; renal function	Dose adjustment; avoid combination hyperkalemic agents
Endothelin antagonists	Fluid retention; edema	Weight; blood pressure	Careful patient selection; diuretic support
Anti-inflammatory agents	GI intolerance (Pentoxifylline)	Renal function; tolerance	Dose modification; adjunctive use

7.2 Translational Challenges

7.2.1 Gaps in Clinical Evidence

Even though renal advantages of the emerging pharmacotherapies have been demonstrated by many clinical trials, there continue to be gaps in the available evidence. Most studies do not include patients with impaired CKD, multimorbidity or older age, making it hard to extrapolate to real-world populations. Moreover, long-term safety data and head-to-head comparisons of novel agents are not readily available, and these aspects make it more difficult to make clinical decisions.

7.2.2 Trial Design Limitations

Traditional clinical trial designs may inadequately capture disease heterogeneity and individual treatment response in CKD. Dependence on surrogate measures like reduction of albumin in the urine or temporary rises in eGFR can not be completely relied on as an indicator of long-term renal outcomes. Adaptive trials and pragmatic trials that include real-world data are also coming to be seen as required to fill the gap between controlled trials and clinical practice [29].

7.3 Future Directions

Individualised nephrology and the use of sophisticated data strategies are the future of renal pharmacotherapy. Clinical, molecular and genetic-based individualised treatment plans can enhance treatment effectiveness with reduced adverse effects. Drug discovery, patient stratification, and prediction of renal outcomes are being popularly used with artificial intelligence and machine learning, which present the possibility to speed up the development of specific therapies and enhance clinical decision support [30]. Collectively, overcoming current clinical challenges will require coordinated efforts across research, regulatory, and clinical domains. Continued innovation in trial design, biomarker development, and digital health integration will be essential to fully realise the promise of emerging renoprotective therapies.

8. Conclusion

The pharmacological renal protection has experienced a significant change in the last decade, where a more multidimensional approach is now implemented, compared to the use of a hemodynamic dimension that is based on a particular direction. Although renin-angiotensin-aldosterone system inhibitors and traditional glycemic control agents are still considered the cornerstones of treatment, the shortcomings of these treatments have highlighted the importance of having supplementary interventions that can combat the underlying renal risk. New pharmacotherapeutic agents, especially the sodium-glucose cotransporter-2 inhibitors and non-steroidal mineralocorticoid receptor antagonists, have shown strong and reliable renoprotective effects in a wide range of patient groups, changing the paradigm of care in nephrology. In addition to these established innovations, new frontiers in treatment, such as endothelin receptor antagonists, anti-inflammatory and anti-fibrotic, targeted biologics, and RNA-based therapies, are promising in further slowing the disease progression by targeting inflammation, fibrosis, metabolic dysfunction, and molecular causes of kidney injury. Combining pharmacogenomics and precision medicine strategies can maximise drug choice, enhance treatment response and reduce drug toxicity, especially in diverse and risky populations with CKD. Although these progresses have been made, there are still significant clinical issues, such as the issue of drug safety, polypharmacy, paucity of long-term outcomes trials, and a lack of evidence on the advanced CKD and real-world populations. This will be improved in future with the enhanced trial designs, biomarker-based therapies, and integrating artificial intelligence in the drug discovery process and clinical decision-making. Together, ongoing innovation and personalised pharmacotherapy will go a long way in ensuring better renal protection and better long-term outcomes of chronic kidney disease patients.

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