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PHARMACOLOGICAL MODULATION OF RENAL BIOCHEMICAL PATHWAYS IN CHRONIC KIDNEY DISEASE: A SYSTEMATIC REVIEW

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ABSTRACT

Background: Chronic kidney disease (CKD) is a complex, progressive disorder driven by interconnected hemodynamic, metabolic, inflammatory, and fibrotic pathways. Traditional therapies largely emphasize risk reduction rather than direct modulation of underlying biochemical mechanisms. Increasing evidence indicates that pathway-targeted pharmacological interventions may offer disease-modifying benefits, necessitating a systematic evaluation of both clinical and mechanistic data.

Methods: A systematic literature review was conducted across peer-reviewed sources published between 2016 and 2025 to assess pharmacological modulation of renal biochemical pathways in CKD. Eligible studies included randomized controlled trials, observational studies, narrative and systematic reviews, experimental investigations, computational analyses, and one doctoral dissertation. Studies involving CKD populations or relevant models and reporting renal clinical or mechanistic outcomes were synthesized using a pathway-based analytical framework.

Results: Twenty-two studies were included, encompassing diabetic and non-diabetic CKD contexts. Pharmacological modulation of the renin–angiotensin–aldosterone system, oxidative stress and fibrotic signalling, and metabolic–mitochondrial pathways was consistently associated with renal protection. SGLT2 inhibitors and non-steroidal mineralocorticoid receptor antagonists demonstrated pleiotropic effects, including attenuation of inflammation, reduction of fibrosis, and slowing of kidney function decline. Evidence also supported combination pharmacotherapy, particularly strategies integrating metabolic and hemodynamic pathway modulation, which showed additive or synergistic reno-protective effects.

Conclusions: This review highlights a transition toward mechanism-informed, multi-pathway pharmacological strategies in CKD management. Targeting convergent biochemical pathways, rather than isolated risk factors, may enhance disease modification. Future research should focus on biomarker-guided precision approaches to optimize therapeutic selection, sequencing, and long-term renal outcomes.

KEYWORDS: Chronic kidney disease; Renal pathways; Pharmacological modulation; SGLT2 inhibitors; Mineralocorticoid receptor antagonists; Combination therapy

1.INTRODUCTION

Chronic kidney disease (CKD) is a significant global health issue impacting a significant percentage of the adult population and leading to a high rate of premature mortality, cardiovascular morbidity and poor quality of life. In addition to its direct effects on the kidneys, CKD is becoming more and more a systemic disorder that may be linked to elevated cardiovascular risk and disrupted metabolism, as well as a condition that may predispose individuals to poor clinical outcomes, and thus a condition that may significantly amplify its total disease burden [1]. Massive epidemiological studies have established that CKD is one of the major causes of disability-adjusted life years in the world, and the global burden is increasing very rapidly due to the upsurge in prevalence rates of diabetes mellitus, hypertension, obesity and metabolic syndrome [2,6]. This is becoming a big burden to the healthcare systems especially in low- and middle-income countries with limited access to early diagnosis and long-term control.

Biochemical and molecular mechanisms that control the development of CKD are complex and interrelated to influence glomerular, tubular, vascular, and interstitial repositories of the kidney. Chronic renin angiotensin aldosterone system activation has a key pathogenic role in the development of diseases, such as facilitating intraglomerular hypertension, endothelial dysfunction, inflammation, and profibrotic signalling. Simultaneously, oxidative stress and low-grade chronic inflammation play a role in the injury of cells, mitochondrial dysfunction, and gradual nephron deterioration [3,5]. Metabolic dysregulation further increases these processes, especially when it comes to obesity and insulin resistance which increases renal injury due to changes in lipid metabolism, oxidative burden and inflammatory signalling pathways [4]. With time, continuous stimulation of fibrotic pathways will result in an extracellular matrix deposition, structural remodelling, and permanent loss of nephrons, finally leading to progressive renal dysfunction. Modern clinical practice guidelines have been focusing on the fact that pharmacological interventions are necessary to manage CKD effectively by directly addressing these underlying pathogenic events along with conventional methods of risk factor control.

In the last 10 years, there have been changes regarding the pharmacological management of CKD. Renin angiotensin system inhibitors have been the mainstay of treatment over the years because they lower proteinuria and delay the course of the disease. Nevertheless, notwithstanding their prevalence, these agents have been shown to have a minimal ability to prevent CKD progression completely, especially in patients who have advanced disease or have various comorbidities. Recently, there is extensive clinical evidence on the use of sodium-glucose co-transporter-2 (SGLT2) inhibitors, which have shown to have extensive renal and cardiovascular protection in a wide range of CKD populations, with or without diabetes [7]. Likewise, it is demonstrated that non-steroidal mineralocorticoid receptor antagonists including finerenone can help to prevent adverse renal and cardiovascular outcomes, especially in diabetic kidney disease patients, which demonstrates the therapeutic value of the target of inflammatory and fibrotic pathways [8].

New information suggests that the reno-protective effects of these new pharmacological agents go far beyond their core effects of action. SGLT2 inhibitors have an effect on the renal hemodynamic effect through a decreased intraglomerular pressure and tubular workload, an increase in metabolic efficiency and a decrease in inflammatory signalling. Simultaneously, mineralocorticoid receptor antagonists are known to suppress inflammation and fibrotic remodelling in the kidney and thus maintain structural and functional integrity [9]. Such complementary processes justify a move to mechanism based and combination approach to therapy in order to address simultaneously various pathways that play a role in the progression of CKD. Along with this progressive insight, emerging views on the efficacy of renal biologic agents indicate the growing significance of new agent usage within comprehensive CKD management strategies, which can enhance favorable and sustainable renal and cardiovascular outcomes [10].

With such relevant contributions to therapy, the literature is still in bits. Functional outcomes like estimated glomerular filtration rate loss, albuminuria, or cardiovascular events are often prioritized in many clinical studies, but little is usually assessed in terms of underlying biochemical and molecular mechanisms that cause such effects [11]. On the other hand, mechanistic and experimental studies tend to study single pathways in isolation, with no apparent connectivity to patient-relevant clinical outcomes or disease progression. Consequently, the synthesis is limited to the extent that a thorough evaluation of the means through which pharmacological interventions regulate renal biochemical pathways and how this regulation can be converted into better renal outcomes at various stages and etiologies of CKD is achieved. This deficiency of integration limits the clarity of mechanistic comparison, complicates and restricts the sensible construction of pathway-directed and mixture treatment regimens.

Mechanistic and clinical evidence should then be incorporated in a systematic literature review that is justified. Such a review can clarify both common and different mechanisms of action, convergent therapeutic targets, and multiple significant gaps in current knowledge by synthesizing the findings of pharmacological classes and renal biochemical pathways. This practice conforms to the developing models of precision medicine in the nephrology field and promotes evidence-based streamlining of therapeutic plans regarding chronic kidney disease, and the eventual aim of enhancing patient outcomes and delaying the progression of the disease.

Objectives

1. To evaluate pharmacological interventions in chronic kidney disease with respect to their effects on key renal biochemical and molecular pathways
2. To synthesize mechanistic and clinical evidence linking pathway modulation to renal functional outcomes and disease progression
3. To identify evidence gaps to guide future research and pathway-targeted therapeutic strategies in chronic kidney disease

2. METHODS

2.1 Protocol and Reporting Standard

This systematic literature review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. A predefined methodological protocol guided all stages of the review process, including study identification, screening, eligibility assessment, and inclusion, to ensure transparency, reproducibility, and methodological rigor. The objective of this review was to systematically evaluate evidence on the pharmacological modulation of renal biochemical pathways in chronic kidney disease (CKD).

2.2 Data Sources and Search Strategy

A comprehensive literature search was performed to identify relevant studies published between January 2016 and December 2025. This period was selected to capture contemporary advances in CKD pharmacotherapy and mechanistic understanding of renal biochemical pathways. Only reliable and openly accessible databases were used. Electronic

searches were conducted in PubMed/MEDLINE, Web of Science, and Google Scholar, which are widely recognized sources for peer-reviewed biomedical research. To enhance completeness, manual reference list screening of eligible full-text articles was also undertaken. The search strategy combined controlled vocabulary and free-text terms related to chronic kidney disease, pharmacological interventions, and renal biochemical pathways. Search terms related to CKD were combined with pharmacological descriptors and pathway-specific terms using Boolean operators. Complete search strategies for all databases were documented and provided as supplementary material.

2.3 Eligibility Criteria

Inclusion Criteria

Studies were eligible for inclusion if they were original peer-reviewed research articles published between 2016 and 2025 that investigated pharmacological interventions in the context of chronic kidney disease. Both human clinical studies and experimental studies employing validated CKD models were included, provided that the intervention directly targeted or modulated renal biochemical or molecular pathways. Eligible studies were required to report kidney-specific outcomes, including clinical measures such as estimated glomerular filtration rate, albuminuria or proteinuria, and serum creatinine, and/or mechanistic outcomes such as molecular or biochemical biomarkers indicative of pathway activity. Only full-text articles published in English were included.

Exclusion Criteria

Studies were excluded if they did not primarily focus on chronic kidney disease or failed to report kidney-specific clinical or mechanistic outcomes. Reviews, editorials, letters, conference abstracts, and case reports were excluded. Studies evaluating non-pharmacological interventions, including dietary or lifestyle modifications or device-based therapies, were not considered eligible. Studies restricted exclusively to dialysis-dependent populations without evaluation of renal biochemical pathways were excluded. Where overlapping datasets were identified, only the most complete and recent publication was retained.

2.4 Study Selection Process

Identification

Studies were identified through systematic searches of PubMed/MEDLINE, Web of Science, and Google Scholar. These searches yielded 320 records, while 30 additional records were identified through manual reference list screening. In total, 350 records were identified. After removal of 70 duplicate records, 280 unique records remained.

Screening

The titles and abstracts of the 280 records were screened for relevance to the review objectives. During this stage, 190 records were excluded because they did not focus on chronic kidney disease, did not involve pharmacological interventions, or failed to evaluate renal biochemical or molecular pathways. Following screening, 90 records were retained for full-text assessment.

Eligibility

Full-text versions of the 90 retained articles were assessed for eligibility. During this stage, 68 studies were excluded for clearly defined reasons. Specifically, 24 studies did not directly examine renal biochemical or molecular pathways, 14 studies demonstrated insufficient methodological or analytical rigor, 16 studies focused on non-renal or tangential therapeutic outcomes, and 14 studies reported incomplete or non-extractable renal outcome data.

Included

After exclusion of these 68 full-text articles, 22 studies met all predefined eligibility criteria and were included in the final synthesis. These studies constituted the evidence base for evaluating pharmacological modulation of renal biochemical pathways and their effects on disease progression and renal outcomes in chronic kidney disease. The study selection process is summarized using a PRISMA 2020 flow diagram in figure 1.

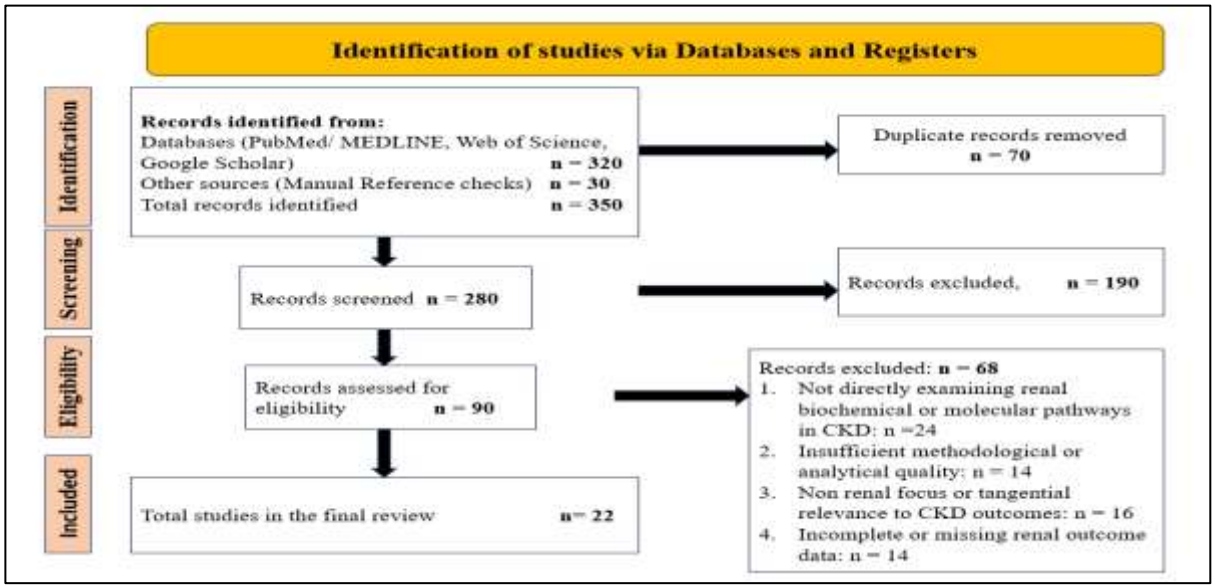

Figure 1. PRISMA Flow Diagram Illustrating the Study Selection Process

2.5 Data Extraction

Data extraction was performed using a standardized and predefined extraction form to ensure consistency. Extracted data included publication details, study design, characteristics of the study population or experimental model, CKD stage or etiology, pharmacological agent and duration of intervention, targeted renal biochemical pathway, and reported clinical and mechanistic outcomes. Key findings relevant to pathway modulation and renal disease progression were systematically recorded.

2.6 Data Synthesis

Due to substantial heterogeneity among included studies with respect to study design, CKD ethology and stage, pharmacological agents, targeted biochemical pathways, and outcome measures, quantitative meta-analysis was not performed. Instead, evidence was synthesized using a structured, pathway-based analytical approach.

Studies were grouped according to the primary renal biochemical pathway targeted by the pharmacological intervention, including modulation of the renin–angiotensin–aldosterone system, oxidative stress and inflammatory signalling, fibrotic pathways, and metabolic or mitochondrial processes. Within each pathway group, findings were evaluated according to pharmacological class, study design, and CKD stage or experimental model.

For each study, the relationship between pathway modulation and kidney-specific outcomes was systematically examined. Clinical outcomes such as estimated glomerular filtration rate, proteinuria or albuminuria, and serum creatinine were assessed alongside molecular, biochemical, or histopathological markers of pathway activity. Consistency and directionality of effects across studies were evaluated to identify pathway-specific therapeutic patterns and mechanistic convergence.

Results were synthesized across studies to highlight common mechanisms of action, differences between pharmacological classes, and potential factors contributing to variability in outcomes, including differences in dosing, treatment duration, and disease severity.

3. RESULTS

3.1 Characteristics of Included Studies

The 22 included studies comprised a diverse range of study designs, including randomized controlled trials, observational studies, narrative and systematic reviews, experimental investigations, computational analyses, and one doctoral dissertation. The included literature reflects contemporary research addressing pharmacological modulation of renal biochemical pathways in chronic kidney disease. Across the studies, multiple pharmacological classes were evaluated, including renin–angiotensin–aldosterone system modulators, sodium–glucose co-transporter-2 inhibitors, mineralocorticoid receptor antagonists, and combination pharmacotherapeutic strategies.

The studies examined chronic kidney disease across different etiologies and clinical contexts, with several focusing specifically on diabetic kidney disease, while others addressed broader CKD populations. Outcomes reported included kidney-specific clinical measures such as estimated glomerular filtration rate, albuminuria or proteinuria, and progression of kidney disease, as well as mechanistic outcomes involving molecular, biochemical, and signalling pathway markers. This diversity enabled a pathway-based synthesis integrating both clinical and mechanistic evidence. The key characteristics of the 22 included studies, encompassing diverse study designs, populations, pharmacological targets, and outcome domains, are presented in Table 1.

Table 1. Characteristics of Included Studies (n = 22)

Study Design	Population / Model	Pharmacological Focus	Primary Outcome Domain	Source
Review	CKD	RAAS modulators	RAAS signalling	[12]
Review	CKD	Multiple agents	Therapeutic overview	[13]
Review	CKD	Antifibrotic agents	Oxidative stress, fibrosis	[14]
Review	CKD	Multiple	Disease overview	[15]
Review	CKD	Multiple	Signalling pathways	[16]
Review	CKD	Multiple	Molecular mechanisms	[17]
Review	CKD	SGLT2 inhibitors	Cardiorenal outcomes	[18]
Review	CKD	SGLT2 inhibitors	Treatment heterogeneity	[19]
Observational	CKD (primary care)	SGLT2 inhibitors	Guideline uptake	[20]
Review	DKD	Multiple	Disease progression	[21]
Review	T2DM-CKD	Multiple	Multifactorial care	[22]
Experimental	Model systems	Canagliflozin	Metabolic pathways	[23]
Computational	CKD	Dapagliflozin	Molecular interactions	[24]
Review	CKD	Finerenone	Mechanism and clinical use	[25]
Review	CKD	Multiple	Pathogenesis, targets	[26]
Review	DKD	Multiple	Molecular mechanisms	[27]
Review	T2DM-CKD	Combination therapy	Cardiorenal protection	[28]
Review	CKD	Aldosterone antagonists	Aldosterone signalling	[29]
Review	Metabolic disease	Metformin	Metabolic pathways	[30]

Network meta-analysis	T2DM-CKD	Finerenone vs SGLT2i	Renal outcomes	[31]
RCT	T2DM	Empagliflozin	CKD progression	[32]
RCT	CKD	Dapagliflozin	Renal outcomes	[33]

3.2 Pharmacological Modulation of Renal Biochemical Pathways

3.2.1 Renin–Angiotensin–Aldosterone System and Aldosterone Signalling

Several studies evaluated pharmacological modulation of the renin–angiotensin–aldosterone system and aldosterone signalling pathways. These studies reported consistent effects on inflammatory, hemodynamic, and fibrotic mechanisms contributing to CKD progression. Mineralocorticoid receptor antagonists, particularly finerenone, demonstrated attenuation of inflammatory and profibrotic signalling. Pharmacological modulation of the renin–angiotensin–aldosterone system and aldosterone signaling pathways and their associated renal outcomes are summarized in Table 2.

Table 2. RAAS and Aldosterone Pathway Modulation

Study	Pharmacological Agent	Targeted Mechanism	Reported Renal Outcomes
[12]	RAAS modulators	RAAS inhibition	↓ proteinuria
[25]	Finerenone	Anti-fibrotic	↓ eGFR decline
[29]	Aldosterone antagonists	Aldosterone signaling	Renal protection
[31]	Finerenone	Fibrosis, inflammation	Improved renal outcomes

3.2.2 Oxidative Stress and Fibrotic Pathway Modulation

Oxidative stress and fibrosis were identified as central biochemical drivers of CKD progression. Pharmacological interventions targeting these pathways were associated with reductions in oxidative damage and extracellular matrix accumulation. Studies addressing oxidative stress and fibrotic pathway modulation and their mechanistic renal effects are summarized in Table 3.

Table 3. Oxidative Stress and Fibrotic Pathway Modulation

Study	Targeted Pathway	Key Mechanistic Findings
[14]	Oxidative stress	↓ ROS, ↓ fibrosis
[17]	Molecular pathways	Structural preservation
[16]	Signaling pathways	Pathway modulation
[26]	Fibrotic signaling	Therapeutic targets

3.2.3 Metabolic and Mitochondrial Pathway Modulation

SGLT2 inhibitors were the most frequently studied pharmacological class targeting metabolic and mitochondrial pathways. These agents consistently demonstrated reno-protective effects across CKD populations. Studies examining metabolic and mitochondrial pathway modulation and their associated renal outcomes are summarized in Table 4.

Table 4. Metabolic and Mitochondrial Pathway Modulation

Study	Pharmacological Agent	Mechanistic Effects	Renal Outcomes
[32]	Empagliflozin	↓ tubular workload	↓ CKD progression
[27]	Dapagliflozin	Metabolic modulation	↓ eGFR decline
[18]	SGLT2 inhibitors	Cardiorenal effects	Renal protection
[24]	Dapagliflozin	Molecular docking	Pathway interaction

3.2.4 Combination Pharmacotherapy

Several studies evaluated combination pharmacotherapy targeting multiple biochemical pathways simultaneously. These approaches demonstrated additive reno-protective effects. Studies evaluating combination pharmacotherapy and multi-pathway modulation strategies and their renal outcomes are summarized in Table 5.

Table 5. Combination Therapy and Multi-Pathway Modulation

Study	Combination Strategy	Targeted Pathways	Reported Outcomes
[28]	SGLT2i + RAAS	Multi-pathway	Enhanced protection
[22]	Multifactorial therapy	Metabolic, inflammatory	Improved outcomes
[31]	Network comparison	Multi-pathway	Superior renal outcomes

4. DISCUSSION

This methodological review of the literature generalizes modern evidence on pharmacological regulation of renal biochemical signatures in chronic kidney disease (CKD) and offers a combined description of the role of these processes in the development and therapy of the disease. The results substantiate the idea that CKD is an uneven and multifactorial condition that is instigated by sophisticated interactions between metabolic disorders, inflammation, fibrosis, genetic vulnerability, and systemic conditions. Therefore, pharmacological interventions which influence inter-related biochemical pathways will have higher chances of altering disease courses as compared to those that act on single mechanisms.

The key interpretation of this review study is that metabolic stress is a crucial factor in the progression of CKD in different etiologies. Modifications of cellular energy metabolism, oxidative homeostasis and mitochondrial activity play roles in tubular damage and nephron progressive loss. Recent developments in therapy focus on these paths of metabolism as an element of more general approaches of reno-protection, as part of a continued trend towards mechanism-based pharmacotherapy, and not symptom-driven approaches [34]. These findings are consistent with the demonstration of the advantages of the agents that enhance renal metabolic efficiency and mitigate the oxidative load, which means that metabolic modulation is a fundamental therapeutic axis in CKD.

The downstream common pathway identified in the studies included was fibrosis regardless of the injury inception. Eventual irreversible kidney damage and subsequent decline in long-term functionality is determined by progressive extracellular matrix deposition and structural remodelling. Initial research on the cellular and molecular genesis of renal fibrosis defined fibrosis as a terminal common pathway in CKD progression, and the critical role of preventing structural damage at the earliest possible stage of disease progression [35]. Current synthesis implies that direct antifibrotic agents still are few, but pharmacological control of upstream metabolic and inflammatory signals can be used to indirectly suppress fibrotic signalling. This justifies a combined treatment strategy where fibrosis is treated by staging the collective pathway regulation in place of targeting separately.

Another major CKD progressor is chronic inflammation and has a close interplay with metabolic and fibrotic processes. Chronic low-grade inflammation is associated with endothelial dysfunction, tubular injury and maladaptive repair responses, which hastens the progression of renal dysfunction. Recently, the renewed reviews of novel therapeutic approaches suggest the role of anti-inflammatory effects as contributors of renoprotection even in the absence of inflammation as a major pharmacological target [36]. In terms of interpolation the findings of this review imply that pleiotropic anti-inflammatory-like therapies have the potential to lessen residual renal risk that remains despite standard therapy.

Systemic CKD means further complications of the disease development and alteration of therapeutic response. Malnutrition and hypercatabolic Cachexia and protein-energy wasting are common in late CKD and are indicative of deep metabolic and inflammatory derangements that are extrarenal. These conditions of the system are closely related to an unfavorable prognosis and can lower the efficiency of pharmacological treatment [37]. The results of this review indicate that therapies with the ability to promote systemic metabolic homeostasis or reduce the strain of inflammatory processes can indirectly reno-protective benefits by targeting these extra-renal causes of disease development.

Genetic predisposition introduces another twist in the CKD pathophysiology. Recent data proves that patients with hereditary kidney diseases are significantly more likely to develop kidney failure, regardless of traditional clinical risk factors [38]. This finding speaks of the weaknesses of generalized treatment approaches and explains the possible significance of incorporating genetic and molecular data into decision-making pharmacology. Genetic risk-based pathology-focused interventions could improve the response of specific CKD cohorts to treatment.

The gut- kidney axis is an emerging and more accepted cause of CKD progression. Changes in the composition of gut microbiota, augmenting intestinal permeability, and oral pathology have a role in systemic inflammation and uremic toxin accumulation and worsen renal injury. The gut dysbiosis-CKD pathophysiology relationship supports the central notion of pathway-based intervention and proposes that future pharmaceutical intercessions might require extra-renal targets to control the disease fully [39].

Although there is an increasing mechanistic insight and therapeutic progress, this review exposes some of the persisting challenges of implementing pathway modulation into long-term clinical advantage. Numerous studies use surrogate biomarkers or short term outcomes and cannot make conclusions about long term disease modification. Synthesis is further complicated by heterogeneity in the study design, outcome measures and mechanistic endpoints. However, all the evidence provides a changing therapeutic paradigm in CKD focusing on combined modulation of metabolic, inflammatory, fibrotic, genetic, and systemic pathways.

This is a system review that shows that pharmacological treatment of CKD needs the multidimensional, pathway-based approach as opposed to a single-mechanism intervention. Further combination of mechanistic understanding, genetic risk classification and systemic illnesses is to be necessary to improve the therapeutic approaches and the long term outcomes of patients with chronic kidney illness.

5. CONCLUSION

This systematic literature review provides a mechanistically grounded perspective on chronic kidney disease, emphasizing conceptual advancement rather than descriptive synthesis. The collective evidence indicates that CKD progression is driven by an integrated network of biochemical disturbances rather than linear, single-pathway dysfunction. Pharmacological interventions that effectively modulate this network particularly those influencing RAAS activity, metabolic stress, oxidative injury, and fibrotic remodelling represent a substantive shift toward biologically informed disease modification. key insight emerging from this review is the expanding therapeutic relevance of pathway pleiotropy. Contemporary agents, notably SGLT2 inhibitors and non-steroidal mineralocorticoid receptor antagonists, demonstrate reno-protective effects that transcend their canonical mechanisms, suggesting convergence on shared downstream signalling hubs governing inflammation, cellular energetics, and tissue repair. This challenges traditional pharmacological paradigms and supports a reclassification of CKD therapies based on mechanistic impact rather than drug class alone. Importantly, the reviewed literature underscores the inadequacy of mono therapeutic strategies in a disease characterized by systemic and cellular complexity. Combination pharmacotherapy, when guided by mechanistic complementarity, emerges as a rational and potentially transformative approach. However, the absence of robust biomarkers to guide therapeutic pairing and sequencing remains a critical translational gap. Future investigations should focus on integrating molecular phenotyping, longitudinal pathway profiling, and adaptive trial designs to refine precision-based treatment

algorithms. Advancing CKD management will require a shift from population-level efficacy toward individualized pathway modulation, thereby aligning pharmacotherapy with the biological heterogeneity that defines disease progression and therapeutic response.

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