Pakistan Journal of Medical & Cardiological Review
https://pakjmcr.com/index.php/1/about
Online ISSN 3007-2387
Print ISSN 3007-2379

Green Extraction of Nephroprotective Phytochemicals for Chronic Kidney Disease: A Pharmacognostic and Pharmacological Review

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Keywords: Chronic Kidney Disease, Nephroprotection, Green Extraction, Phytochemicals, Ultrasound-Assisted Extraction, Supercritical Fluid Extraction, Pharmacognosy.

Received on 25 Dec 2025
Accepted on 27 Jan 2026
Published on 07 Feb 2026

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Abstract

Chronic Kidney Disease (CKD) is a major global health burden characterized by progressive loss of renal function and high morbidity. Traditional pharmacological therapies are often limited by side effects and inadequate disease modification, prompting significant interest in plant-derived bioactive compounds with nephroprotective properties. Recent advances in green extraction technologies — including ultrasound-assisted extraction (UAE), microwave-assisted extraction (MAE), and supercritical fluid extraction (SFE) — offer sustainable, efficient methods to isolate potent phytochemicals while minimizing environmental impact. Green extractions enhance yield and preserve pharmacological integrity of compounds such as flavonoids, polyphenols, terpenoids, and other nephroprotective metabolites, essential for therapeutic development. Importantly, multiple clinical trials and preclinical studies demonstrate that plant-derived bioactive compounds can modulate pathways implicated in CKD pathogenesis, including oxidative stress, inflammation, fibrosis, apoptosis and uremic toxin accumulation. Common nephroprotective agents include curcumin, catechins, rhein, flavonoids, and saponins extracted from species such as *Camellia sinensis*, *Rheum* spp., *Curcuma longa*, and others, which exhibit antioxidant, anti-inflammatory, anti-fibrotic, and renal function-preserving effects. While conventional extraction methods have yielded valuable data, modern green extraction techniques maximize bioactive compound yield and selectivity with reduced organic

solvent use and energy consumption, aligning with environmental sustainability goals. This review synthesizes phytochemical profiles of nephroprotective plants, compares green extraction methodologies, and explores the pharmacological mechanisms through which these phytochemicals may mitigate CKD progression. We also discuss challenges including standardization, bioavailability, clinical translation, and regulatory considerations necessary to advance these phytochemicals to therapeutic application. Collectively, green extraction of nephroprotective phytochemicals represents a promising intersection of sustainable technology and evidence-based therapeutics in the management of CKD.

Introduction

Chronic Kidney Disease (CKD) is a progressive and irreversible disorder characterized by structural and functional impairment of the kidneys, leading to a sustained reduction in glomerular filtration rate (GFR) and accumulation of metabolic waste products. CKD represents a major global public health challenge, affecting more than 10% of the world's population and contributing significantly to cardiovascular morbidity, disability, and premature mortality (Hill et al., 2016; Jager et al., 2019). Despite advances in renal replacement therapies and pharmacological management, CKD remains largely incurable, with current interventions primarily focused on slowing disease progression rather than reversing renal damage.

The pathogenesis of CKD is multifactorial and involves persistent oxidative stress, chronic inflammation, endothelial dysfunction, apoptosis, fibrosis, and dysregulation of cellular signaling pathways such as nuclear factor-κB (NF-κB), transforming growth factor-β (TGF-β), and renin–angiotensin–aldosterone system (RAAS) signaling (Ruiz-Ortega et al., 2020). These mechanisms collectively lead to progressive nephron loss, tubulointerstitial fibrosis, and glomerulosclerosis. Conventional pharmacotherapies, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and sodium–glucose cotransporter-2 inhibitors, provide partial renoprotection but are often limited by adverse effects, residual risk, and high economic burden (Heerspink et al., 2020). Consequently, there is increasing interest in complementary and alternative therapeutic strategies that target multiple pathogenic pathways with improved safety profiles.

Medicinal plants have been used for centuries in traditional systems of medicine for the management of renal disorders. In recent decades, scientific evidence has increasingly supported the nephroprotective potential of plant-derived bioactive compounds, including flavonoids, phenolic acids, terpenoids, alkaloids, saponins, and polysaccharides (Tienda-Vázquez et al., 2022). These phytochemicals exert renoprotective effects through antioxidant, anti-inflammatory, anti-fibrotic, anti-apoptotic, and immunomodulatory mechanisms, making them particularly relevant for a complex, multifactorial disease such as CKD. Preclinical and clinical studies have demonstrated that compounds such as curcumin, catechins, resveratrol, rhein, quercetin, and epigallocatechin gallate can attenuate renal injury and improve biochemical and histopathological parameters in CKD models (Li et al., 2021; Josa et al., 2024).

Pharmacognosy plays a critical role in the development of plant-based nephroprotective agents by ensuring correct botanical identification, quality control, phytochemical characterization, and standardization of herbal materials. However, the therapeutic efficacy of phytochemicals is highly dependent on extraction methodology, as conventional extraction techniques often involve excessive use of organic solvents, prolonged extraction times, thermal degradation of bioactive compounds, and environmental toxicity (Chemat et al., 2019). These limitations have driven the development of green extraction technologies, which align with principles of sustainability, efficiency, and preservation of phytochemical integrity.

Green extraction techniques, including ultrasound-assisted extraction (UAE), microwave-assisted extraction (MAE), supercritical fluid extraction (SFE), and pressurized liquid extraction (PLE), have emerged as innovative alternatives to traditional extraction methods. These approaches reduce solvent consumption, energy requirements, and processing time while enhancing extraction yield, selectivity, and reproducibility (Chemat et al., 2019; Mustafa & Turner, 2011). Importantly, green extraction methods are particularly advantageous for isolating thermolabile and oxidation-sensitive nephroprotective phytochemicals, thereby improving their pharmacological potential and translational applicability.

The integration of green extraction technologies with pharmacognostic and pharmacological research offers a promising framework for the sustainable development of nephroprotective therapeutics. By optimizing extraction parameters and ensuring standardized phytochemical profiles, these techniques facilitate the generation of high-quality herbal extracts suitable for preclinical and clinical investigation. Furthermore, the use of environmentally benign solvents such as water, ethanol, and supercritical carbon dioxide aligns with regulatory expectations and supports scalability for pharmaceutical and nutraceutical applications.

Despite growing interest in plant-based interventions for CKD, a comprehensive synthesis that integrates nephroprotective phytochemicals, their pharmacological mechanisms, and the role of green extraction technologies remains limited. Existing reviews often focus either on medicinal plants or extraction techniques in isolation, without addressing how sustainable extraction methodologies can enhance the therapeutic efficacy and translational potential of nephroprotective compounds. Therefore, a holistic evaluation that bridges pharmacognosy, green chemistry, and renal pharmacology is urgently needed.

This review aims to critically examine nephroprotective phytochemicals relevant to CKD and evaluate green extraction techniques used for their isolation. Emphasis is placed on pharmacognostic characterization, extraction efficiency, pharmacological mechanisms of action, and available preclinical and clinical evidence. By integrating sustainable extraction strategies with mechanistic insights into renal protection, this review seeks to provide a scientific foundation for the future development of safe, effective, and environmentally responsible phytotherapeutic interventions for CKD.

Pathophysiology of Chronic Kidney Disease and Molecular Targets for Nephroprotective Phytochemicals

Chronic Kidney Disease (CKD) is characterized by a sustained decline in renal function resulting from progressive structural and functional damage to nephrons. The disease evolves through complex and interconnected molecular mechanisms involving oxidative stress, chronic inflammation, endothelial dysfunction, fibrosis, apoptosis, mitochondrial impairment, and dysregulation of cellular signaling pathways. Understanding these pathological processes is essential for identifying therapeutic targets that may be modulated by nephroprotective phytochemicals.

Oxidative Stress and Reactive Oxygen Species

Oxidative stress is a central contributor to CKD progression and results from an imbalance between the generation of reactive oxygen species (ROS) and the antioxidant defense system. In CKD, excessive ROS production originates from mitochondrial dysfunction, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activation, and impaired antioxidant enzyme activity. Elevated ROS levels lead to lipid peroxidation, protein oxidation, DNA damage, and cellular dysfunction within renal tubular epithelial cells and glomerular structures (Duni et al., 2019).

Oxidative stress promotes renal injury by activating redox-sensitive transcription factors such as nuclear factor erythroid 2–related factor 2 (Nrf2) and NF-κB. While Nrf2 activation initially induces antioxidant gene expression, chronic oxidative stress

ultimately overwhelms protective mechanisms, leading to sustained inflammation and fibrosis. Nephroprotective phytochemicals such as flavonoids, polyphenols, and phenolic acids exert antioxidant effects by scavenging free radicals, enhancing endogenous antioxidant enzymes (superoxide dismutase, catalase, glutathione peroxidase), and restoring redox homeostasis (Li et al., 2021).

Chronic Inflammation and Immune Dysregulation

Chronic low-grade inflammation is a hallmark of CKD and is closely linked to oxidative stress. Persistent renal injury activates immune cells, including macrophages and T lymphocytes, which infiltrate renal tissue and release pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6). These cytokines amplify inflammatory cascades, exacerbate endothelial dysfunction, and promote further nephron loss (Ruiz-Ortega et al., 2020).

NF-κB signaling plays a pivotal role in mediating inflammatory responses in CKD. Sustained activation of NF-κB induces transcription of cytokines, chemokines, adhesion molecules, and pro-fibrotic mediators. Several plant-derived bioactive compounds, including curcumin, quercetin, and resveratrol, have demonstrated the ability to inhibit NF-κB activation, thereby attenuating inflammation and slowing CKD progression in experimental models (Josa et al., 2024).

Renal Fibrosis and Extracellular Matrix Accumulation

Renal fibrosis represents the final common pathway of CKD regardless of etiology and is characterized by excessive accumulation of extracellular matrix (ECM) proteins, including collagen I, collagen III, and fibronectin. Fibrosis results from the activation of fibroblasts and myofibroblasts, epithelial-to-mesenchymal transition (EMT), and dysregulated wound healing responses (Humphreys, 2018).

Transforming growth factor-β (TGF-β) is the principal pro-fibrotic cytokine driving renal fibrosis. TGF-β signaling activates Smad-dependent and Smad-independent pathways, leading to increased ECM synthesis and inhibition of matrix degradation. Persistent TGF-β activation promotes irreversible scarring and loss of functional renal tissue. Nephroprotective phytochemicals such as catechins, rhein, and saponins have been shown to downregulate TGF-β expression, inhibit Smad signaling, and reduce fibrotic changes in renal tissue (Tienda-Vázquez et al., 2022).

Apoptosis and Tubular Cell Loss

Apoptosis of renal tubular epithelial cells is a critical event in CKD progression and contributes to tubular atrophy and interstitial fibrosis. Pro-apoptotic signaling pathways, including mitochondrial cytochrome c release, caspase activation, and p53 signaling, are upregulated in response to oxidative stress, inflammation, and ischemic injury. Excessive apoptosis compromises nephron integrity and accelerates functional decline (Venkatachalam et al., 2015).

Several phytochemicals exhibit anti-apoptotic effects by modulating B-cell lymphoma-2 (Bcl-2) family proteins, inhibiting caspase activation, and preserving mitochondrial membrane potential. These effects highlight the therapeutic relevance of plant-derived compounds in preserving renal cellular architecture.

Endothelial Dysfunction and Microvascular Injury

Endothelial dysfunction is an early and progressive feature of CKD and contributes to impaired renal perfusion, hypoxia, and glomerular damage. Reduced nitric oxide (NO) bioavailability, increased oxidative stress, and inflammatory activation disrupt endothelial homeostasis. Microvascular rarefaction further exacerbates renal hypoxia, creating a vicious cycle that accelerates disease progression (Kang et al., 2020).

Certain phytochemicals, including polyphenols and flavonoids, improve endothelial function by enhancing NO synthesis, reducing oxidative stress, and suppressing inflammatory signaling. These vascular-protective effects may indirectly contribute to nephroprotection.

Uremic Toxins and Metabolic Disturbances

As renal function declines, uremic toxins such as indoxyl sulfate, p-cresyl sulfate, and advanced glycation end products accumulate in the bloodstream. These toxins exert direct nephrotoxic effects, induce oxidative stress, promote inflammation, and worsen cardiovascular outcomes. Importantly, uremic toxins activate aryl hydrocarbon receptor (AhR) signaling, contributing to renal fibrosis and systemic toxicity (Vanholder et al., 2018).

Emerging evidence suggests that certain plant-derived compounds can reduce uremic toxin production, enhance intestinal barrier integrity, and modulate gut microbiota, thereby alleviating toxin-mediated renal injury.

Therapeutic Implications for Phytochemical Intervention

The multifactorial pathogenesis of CKD underscores the limitations of single-target pharmacological therapies and highlights the potential advantages of multi-target phytochemicals. By simultaneously modulating oxidative stress, inflammation, fibrosis, apoptosis, and endothelial dysfunction, nephroprotective phytochemicals offer a holistic therapeutic strategy. When combined with optimized green extraction technologies, these compounds can be obtained with higher purity, stability, and biological activity, enhancing their translational potential.

Nephroprotective Phytochemicals: Classes, Botanical Sources, and Renal Protective Effects

Plant-derived bioactive compounds represent a diverse group of secondary metabolites that exert nephroprotective effects through multiple molecular mechanisms relevant to Chronic Kidney Disease (CKD). These compounds are broadly classified into phenolic compounds, flavonoids, terpenoids, alkaloids, saponins, and polysaccharides. Their multitarget actions are particularly advantageous in CKD, where oxidative stress, inflammation, fibrosis, apoptosis, and metabolic dysregulation coexist. Importantly, the efficiency and integrity of these phytochemicals are strongly influenced by extraction methodology, making green extraction techniques central to their therapeutic development.

Phenolic Compounds and Polyphenols

Phenolic compounds are among the most extensively studied nephroprotective phytochemicals due to their strong antioxidant and anti-inflammatory properties. Structurally characterized by one or more hydroxylated aromatic rings, polyphenols neutralize reactive oxygen species (ROS), chelate metal ions, and modulate redox-sensitive signaling pathways.

Epigallocatechin-3-gallate (EGCG), a major catechin from Camellia sinensis, has demonstrated significant renoprotective effects in experimental CKD models. EGCG attenuates oxidative stress by upregulating Nrf2-mediated antioxidant enzymes while simultaneously suppressing NF-κB-driven inflammatory cascades. Preclinical studies report reductions in serum creatinine, blood urea nitrogen, and histopathological damage following EGCG administration (Josa et al., 2024).

Resveratrol, a stilbene polyphenol found in Vitis vinifera and several medicinal plants, exhibits protective effects against renal ischemia-reperfusion injury and CKD progression. Its mechanisms include activation of sirtuin-1 (SIRT1), inhibition of inflammatory cytokine production, and suppression of renal fibrosis via TGF-β modulation (Li et al., 2021).

Green extraction approaches such as ultrasound-assisted extraction (UAE) and pressurized liquid extraction (PLE) have proven particularly effective for isolating polyphenols while preserving their redox activity and minimizing solvent toxicity.

Flavonoids

Flavonoids constitute a major subgroup of polyphenols and are widely distributed in medicinal plants with nephroprotective relevance. These compounds exert renoprotective effects primarily through antioxidant, anti-apoptotic, and anti-fibrotic mechanisms.

Quercetin, present in Allium cepa, Moringa oleifera, and several traditional medicinal herbs, has been shown to mitigate renal oxidative injury by restoring glutathione levels and suppressing lipid peroxidation. Additionally, quercetin downregulates pro-fibrotic mediators such as collagen I and α-smooth muscle actin, thereby limiting tubulointerstitial fibrosis (Tienda-Vázquez et al., 2022).

Rutin, another flavonoid glycoside, demonstrates vascular-protective and anti-inflammatory effects in CKD by improving endothelial nitric oxide bioavailability and reducing microvascular injury. Microwave-assisted extraction (MAE) has been shown to significantly enhance flavonoid yield compared with conventional solvent extraction while reducing processing time and energy consumption (Chemat et al., 2019).

Curcuminoids

Curcuminoids, particularly curcumin derived from Curcuma longa, represent one of the most extensively investigated phytochemicals in renal pharmacology. Curcumin exhibits potent anti-inflammatory activity by inhibiting NF-κB signaling, suppressing TNF-α and IL-6 production, and reducing oxidative stress through enhancement of antioxidant enzymes.

In CKD models, curcumin attenuates renal fibrosis by downregulating TGF-β/Smad signaling and inhibiting epithelial-to-mesenchymal transition. Clinical studies in CKD and dialysis patients report improvements in inflammatory markers and oxidative stress parameters following curcumin supplementation (Josa et al., 2024).

Supercritical fluid extraction (SFE) using carbon dioxide has emerged as an optimal green technique for curcuminoid isolation, yielding high-purity extracts with minimal thermal degradation and solvent residue.

Anthraquinones and Related Compounds

Anthraquinones such as rhein and emodin, primarily isolated from Rheum officinale and Polygonum multiflorum, exhibit notable nephroprotective properties at controlled doses. Rhein has been shown to reduce proteinuria, inhibit mesangial cell proliferation, and suppress inflammatory cytokine expression.

Mechanistically, anthraquinones modulate TGF-β signaling, inhibit oxidative stress, and enhance renal excretion of uremic toxins. However, their therapeutic application requires careful standardization due to dose-dependent nephrotoxicity risks. Green extraction techniques such as PLE allow precise control over extraction conditions, improving safety and reproducibility (Tienda-Vázquez et al., 2022).

Saponins and Terpenoids

Saponins and terpenoids represent another important class of nephroprotective phytochemicals. Triterpenoid saponins from Boerhavia diffusa (Punarnava) have demonstrated diuretic, anti-inflammatory, and antioxidant activities, contributing to improved renal clearance and reduced interstitial inflammation.

Terpenoids such as andrographolide from Andrographis paniculata exert protective effects against nephrotoxicity by suppressing inflammatory mediators and preserving

mitochondrial function. UAE and MAE are particularly effective for extracting these compounds while maintaining structural integrity.

Polysaccharides

Plant-derived polysaccharides exhibit immunomodulatory and antioxidant effects that contribute indirectly to nephroprotection. Polysaccharides isolated from medicinal fungi and herbs enhance antioxidant defenses, reduce inflammatory signaling, and modulate gut microbiota, thereby decreasing uremic toxin production (Vanholder et al., 2018).

Green extraction methods such as hot-water extraction combined with ultrasound assistance improve polysaccharide yield and bioactivity while minimizing chemical degradation.

Table 1. Major Nephroprotective Phytochemicals, Botanical Sources, and Mechanisms

Phytochemical Class	Representative Compound	Botanical Source	Key Renal Protective Mechanisms	Preferred Green Extraction
Polyphenols	EGCG	*Camellia sinensis*	Antioxidant, anti-inflammatory, Nrf2 activation	UAE, PLE
Flavonoids	Quercetin	*Moringa oleifera*	Anti-fibrotic, anti-apoptotic	MAE
Curcuminoids	Curcumin	*Curcuma longa*	NF-κB inhibition, anti-fibrotic	SFE
Anthraquinones	Rhein	*Rheum officinale*	Anti-proteinuric, TGF-β suppression	PLE
Saponins	Boeravinones	*Boerhavia diffusa*	Diuretic, antioxidant	UAE
Terpenoids	Andrographolide	*Andrographis paniculata*	Anti-inflammatory, mitochondrial protection	MAE

Green Extraction Technologies for Nephroprotective Phytochemicals

The therapeutic efficacy and translational potential of nephroprotective phytochemicals are strongly influenced by the extraction method employed. Conventional extraction techniques, such as maceration, Soxhlet extraction, and refluxing, often require large volumes of organic solvents, prolonged extraction times, and elevated temperatures, which can degrade thermolabile compounds and generate environmentally hazardous waste. In contrast, green extraction technologies emphasize sustainability, efficiency, selectivity, and preservation of bioactivity, making them particularly suitable for isolating nephroprotective compounds intended for long-term use in Chronic Kidney Disease (CKD) management.

Green extraction is defined by reduced solvent and energy consumption, use of safe and renewable solvents, improved extraction yield, and minimized environmental impact. These technologies align with modern regulatory expectations and pharmaceutical quality standards while enabling reproducible pharmacognostic standardization (Chemat et al., 2019).

Principles of Green Extraction

The concept of green extraction is guided by six core principles:

(1) selection of renewable plant resources;

(2) use of alternative, environmentally benign solvents;

(3) reduction in energy consumption;

(4) minimization of extraction time;

(5) enhancement of selectivity and yield; and

(6) generation of biodegradable byproducts.

For nephroprotective phytochemicals—many of which are polyphenolic, thermolabile, and oxidation-sensitive—green extraction methods preserve molecular integrity while maintaining pharmacological potency. This is particularly relevant for compounds targeting oxidative stress, inflammation, and fibrosis, where structural modifications can significantly alter biological activity.

Ultrasound-Assisted Extraction (UAE)

Ultrasound-assisted extraction (UAE) utilizes high-frequency sound waves (20–100 kHz) to generate cavitation bubbles in the extraction solvent. The collapse of these bubbles produces microjets and shock waves that disrupt plant cell walls, enhancing solvent penetration and mass transfer.

UAE offers several advantages for nephroprotective phytochemicals:

Reduced extraction time

Lower solvent usage

Improved extraction yield

Preservation of thermolabile compounds

UAE has been successfully applied to extract flavonoids, phenolic acids, saponins, and polysaccharides from nephroprotective plants. For example, UAE-enhanced extraction of catechins and quercetin derivatives demonstrates higher antioxidant activity compared to conventionally extracted counterparts. This enhanced bioactivity is particularly relevant for mitigating oxidative stress and inflammation in CKD (Chemat et al., 2019).

However, excessive ultrasound intensity may induce localized heating and free radical formation, potentially degrading sensitive compounds. Therefore, optimization of amplitude, extraction time, and solvent composition is essential.

Microwave-Assisted Extraction (MAE)

Microwave-assisted extraction (MAE) employs microwave radiation to rapidly heat polar solvents and plant matrices through dipole rotation and ionic conduction. This rapid heating causes internal pressure buildup within plant cells, leading to cell wall rupture and efficient release of intracellular phytochemicals.

MAE is particularly effective for extracting flavonoids, curcuminoids, and phenolic compounds with high polarity. Compared to UAE, MAE often achieves higher extraction efficiency in significantly shorter timeframes. Studies report superior yields of quercetin, rutin, and curcumin using MAE with aqueous ethanol as a green solvent (Mustafa & Turner, 2011).

In the context of CKD therapeutics, MAE-derived extracts demonstrate enhanced anti-inflammatory and antioxidant activities, attributed to improved preservation of functional hydroxyl groups. However, careful temperature control is necessary, as overheating may degrade heat-sensitive nephroprotective compounds.

Supercritical Fluid Extraction (SFE)

Supercritical fluid extraction (SFE), most commonly using supercritical carbon dioxide (SC-CO_2), represents one of the most advanced green extraction technologies. When CO_2 is subjected to conditions above its critical temperature (31.1 °C) and

pressure (73.8 bar), it exhibits both gas-like diffusivity and liquid-like solvating power.

SFE offers exceptional advantages:

Non-toxic, residue-free solvent

High selectivity

Low extraction temperature

Excellent preservation of bioactivity

SFE is particularly suitable for extracting lipophilic nephroprotective compounds such as curcuminoids, terpenoids, and certain phenolic fractions. For example, SFE-extracted curcumin exhibits superior purity, stability, and anti-inflammatory activity compared to solvent-extracted forms, making it highly suitable for long-term CKD interventions (Chemat et al., 2019).

The main limitation of SFE is the high initial equipment cost and requirement for technical expertise. Nevertheless, its scalability and pharmaceutical compatibility make it attractive for clinical-grade extract production.

Pressurized Liquid Extraction (PLE)

Pressurized liquid extraction (PLE), also known as accelerated solvent extraction, employs elevated temperature and pressure to maintain solvents in a liquid state beyond their boiling point. This enhances solubility, diffusion, and extraction kinetics without excessive solvent consumption.

PLE is highly effective for extracting polyphenols, anthraquinones, and glycosides from nephroprotective plants. By fine-tuning temperature and pressure parameters, PLE enables selective extraction while minimizing degradation. Importantly, PLE allows precise standardization of extracts—an essential requirement for reproducible pharmacological studies and regulatory approval (Mustafa & Turner, 2011).

In CKD-focused research, PLE has been employed to extract rhein and related anthraquinones with improved safety and consistency compared to traditional methods.

Solvent Selection in Green Extraction

The choice of solvent plays a critical role in green extraction efficiency. Water, ethanol, and ethanol–water mixtures are preferred due to their low toxicity, biodegradability, and regulatory acceptance. Supercritical CO_2 further eliminates solvent residue concerns, making it ideal for pharmaceutical and nutraceutical applications.

For nephroprotective phytochemicals intended for chronic administration, solvent safety is particularly important to minimize cumulative toxicity risks.

Comparative Evaluation of Green Extraction Techniques

Table 2. Comparison of Green Extraction Techniques for Nephroprotective Phytochemicals

Extraction Technique	Solvent Type	Temperature	Selectivity	Suitability for CKD Phytochemicals	Key Advantages	Limitations
UAE	Water / Ethanol	Low–Moderate	Moderate	Flavonoids, polyphenols	Low energy, fast	Optimization required
MAE	Polar solvents	Moderate–High	High	Curcuminoids, flavonoids	Very rapid extraction	Thermal risk
SFE	CO_2	Low	Very	Terpenoids,	High purity,	High cost

Extraction Technique	Solvent Type	Temperature	Selectivity	Suitability for CKD Phytochemicals	Key Advantages	Limitations
			High	curcumin	solvent-free	
PLE	Water / Ethanol	Moderate	High	Anthraquinones, phenolics	Reproducible, scalable	Equipment cost

Relevance of Green Extraction to Translational Nephroprotection

Green extraction technologies bridge the gap between traditional herbal medicine and evidence-based renal pharmacotherapy. By ensuring consistent phytochemical profiles, enhanced bioactivity, and environmental sustainability, these techniques support the development of standardized nephroprotective agents suitable for preclinical testing and clinical trials in CKD populations.

Pharmacological Mechanisms of Nephroprotective Phytochemicals Extracted via Green Technologies

Nephroprotective phytochemicals exert their therapeutic effects through multiple, interconnected pharmacological mechanisms that directly target the molecular pathways involved in Chronic Kidney Disease (CKD) pathogenesis. The multifactorial nature of CKD—encompassing oxidative stress, inflammation, fibrosis, apoptosis, endothelial dysfunction, and uremic toxicity—necessitates multi-target therapeutic approaches. Phytochemicals extracted using green technologies are particularly advantageous, as these methods preserve structural integrity, bioavailability, and biological potency, thereby enhancing pharmacological efficacy.

Antioxidant Defense and Redox Homeostasis

Oxidative stress is a primary driver of CKD progression and contributes to renal cell injury through excessive production of reactive oxygen species (ROS). Nephroprotective phytochemicals mitigate oxidative damage by both direct and indirect antioxidant mechanisms.

Polyphenols and flavonoids act as free radical scavengers through hydrogen atom donation and electron transfer, thereby neutralizing superoxide anions, hydroxyl radicals, and peroxynitrite. More importantly, many phytochemicals activate the nuclear factor erythroid 2–related factor 2 (Nrf2) pathway, a master regulator of antioxidant gene expression. Activation of Nrf2 leads to upregulation of phase II detoxifying and antioxidant enzymes such as heme oxygenase-1 (HO-1), superoxide dismutase (SOD), catalase, and glutathione peroxidase (Duni et al., 2019).

Green extraction methods, particularly ultrasound-assisted extraction (UAE) and pressurized liquid extraction (PLE), preserve hydroxyl groups and conjugated ring structures essential for antioxidant activity. Consequently, green-extracted phytochemicals demonstrate superior redox-modulating capacity compared to conventionally extracted compounds.

Anti-Inflammatory Modulation of Cytokine Signaling

Chronic inflammation is a hallmark of CKD and is sustained by persistent activation of inflammatory signaling pathways, particularly nuclear factor-κB (NF-κB). NF-κB activation induces transcription of pro-inflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6), which perpetuate renal injury and fibrosis.

Phytochemicals such as curcumin, quercetin, resveratrol, and epigallocatechin gallate suppress NF-κB activation by inhibiting IκB kinase phosphorylation and preventing nuclear translocation of NF-κB subunits. This results in reduced cytokine production, diminished macrophage infiltration, and attenuation of tubulointerstitial inflammation (Josa et al., 2024).

Green extraction techniques enhance the anti-inflammatory potency of these compounds by minimizing oxidative degradation and solvent-induced structural modifications, thereby preserving functional moieties responsible for cytokine inhibition.

Anti-Fibrotic Effects and TGF-β/Smad Pathway Inhibition

Renal fibrosis is the final common pathological endpoint of CKD and is driven primarily by transforming growth factor-β (TGF-β) signaling. TGF-β activates Smad2/3 transcription factors, leading to increased synthesis of extracellular matrix (ECM) proteins and suppression of matrix degradation.

Several nephroprotective phytochemicals directly interfere with TGF-β signaling. Curcumin, catechins, rhein, and certain saponins inhibit TGF-β expression, block Smad phosphorylation, and suppress epithelial-to-mesenchymal transition (EMT) in renal tubular cells. This results in reduced collagen deposition, attenuation of fibroblast activation, and preservation of renal architecture (Humphreys, 2018).

Supercritical fluid extraction (SFE) has been shown to yield high-purity anti-fibrotic compounds with enhanced stability, making it particularly suitable for producing clinically relevant nephroprotective extracts.

Anti-Apoptotic and Mitochondrial Protective Mechanisms

Apoptosis of renal tubular epithelial cells accelerates nephron loss and contributes to CKD progression. Phytochemicals exert anti-apoptotic effects by modulating intrinsic mitochondrial pathways, including regulation of B-cell lymphoma-2 (Bcl-2) family proteins and inhibition of caspase activation.

Compounds such as quercetin and resveratrol stabilize mitochondrial membrane potential, reduce cytochrome c release, and suppress caspase-3 and caspase-9 activation. Additionally, activation of AMP-activated protein kinase (AMPK) and sirtuin-1 (SIRT1) pathways enhances mitochondrial biogenesis and energy homeostasis, thereby protecting renal cells from metabolic stress (Li et al., 2021).

Green extraction preserves mitochondrial-protective phytochemical fractions that may otherwise be degraded during prolonged conventional extraction processes.

Improvement of Endothelial Function and Microcirculation

Endothelial dysfunction is a critical contributor to renal hypoxia and microvascular injury in CKD. Reduced nitric oxide (NO) bioavailability, increased oxidative stress, and inflammation impair endothelial signaling and renal perfusion.

Polyphenols and flavonoids improve endothelial function by enhancing endothelial nitric oxide synthase (eNOS) activity, reducing oxidative inactivation of NO, and suppressing vascular inflammation. Improved microcirculation alleviates renal hypoxia, reduces ischemic injury, and indirectly slows CKD progression (Kang et al., 2020).

Green extraction enhances endothelial-protective effects by maintaining compound bioavailability and reducing solvent residues that may interfere with vascular signaling.

Modulation of Uremic Toxins and Gut–Kidney Axis

Accumulation of protein-bound uremic toxins such as indoxyl sulfate and p-cresyl sulfate exacerbates oxidative stress, inflammation, and fibrosis in CKD. These toxins activate the aryl hydrocarbon receptor (AhR), promoting renal and systemic toxicity.

Emerging evidence suggests that certain phytochemicals modulate the gut microbiota, reducing production of uremic toxins and enhancing intestinal barrier integrity. Polyphenols and polysaccharides act as prebiotics, altering microbial metabolism and decreasing toxin generation. This gut–kidney axis modulation represents an important indirect nephroprotective mechanism (Vanholder et al., 2018).
Green extraction ensures that high-molecular-weight polysaccharides and microbiota-modulating compounds retain their structural functionality.

Synergistic and Multi-Target Pharmacological Effects
A defining advantage of nephroprotective phytochemicals is their ability to act on multiple pathological pathways simultaneously. Unlike single-target synthetic drugs, phytochemicals provide synergistic antioxidant, anti-inflammatory, anti-fibrotic, and metabolic regulatory effects. When extracted using green technologies, these compounds demonstrate improved consistency, reproducibility, and translational relevance.

Table 3. Key Pharmacological Mechanisms of Green-Extracted Nephroprotective Phytochemicals

Pathological Target	Molecular Pathway	Representative Phytochemicals	Extraction Method
Oxidative stress	Nrf2–HO-1	EGCG, quercetin	UAE, PLE
Inflammation	NF-κB inhibition	Curcumin, resveratrol	MAE, SFE
Fibrosis	TGF-β/Smad suppression	Rhein, catechins	PLE
Apoptosis	Bcl-2 / Caspase inhibition	Quercetin	UAE
Endothelial dysfunction	eNOS activation	Polyphenols	MAE
Uremic toxins	AhR modulation	Polysaccharides	UAE

Preclinical and Clinical Evidence of Green-Extracted Nephroprotective Phytochemicals
The translational relevance of nephroprotective phytochemicals depends on robust preclinical validation and well-designed clinical studies. Evidence accumulated over the last decade indicates that phytochemicals extracted through green technologies demonstrate superior biological activity, safety, and reproducibility compared to conventionally extracted counterparts. These findings are particularly relevant for chronic, progressive conditions such as Chronic Kidney Disease (CKD), where long-term safety and multi-target efficacy are essential.

Evidence from In Vitro Renal Cell Models
In vitro models provide mechanistic insight into nephroprotection at the cellular and molecular level. Commonly used systems include human proximal tubular epithelial cells (HK-2), podocytes, mesangial cells, and renal fibroblasts exposed to nephrotoxic stimuli such as cisplatin, high glucose, indoxyl sulfate, and hydrogen peroxide.
Green-extracted polyphenols and flavonoids consistently demonstrate cytoprotective effects by reducing oxidative stress, suppressing inflammatory signaling, and preserving mitochondrial integrity. Studies comparing extraction methods show that ultrasound-assisted and microwave-assisted extracts exhibit higher antioxidant capacity, greater Nrf2 activation, and stronger inhibition of NF-κB signaling than solvent-based extracts. This superiority is attributed to improved preservation of hydroxylated phenolic structures and reduced thermal degradation.

In podocyte injury models, green-extracted catechins and quercetin attenuate actin cytoskeleton disruption and reduce apoptosis by regulating AMPK–SIRT1 signaling. These effects are crucial, as podocyte loss is an early determinant of proteinuria and CKD progression.

Animal Models of Nephroprotection

Chemically Induced Nephrotoxicity Models

Rodent models using cisplatin, gentamicin, or adenine are widely employed to study acute kidney injury (AKI) progressing to CKD. In these models, green-extracted phytochemicals consistently reduce serum creatinine, blood urea nitrogen (BUN), and histopathological damage.

Curcumin and resveratrol extracted via supercritical fluid or pressurized liquid extraction show enhanced bioavailability and greater suppression of tubular necrosis, oxidative stress markers, and inflammatory cytokines compared with conventionally extracted preparations. These compounds downregulate TNF-α, IL-6, and MCP-1 while upregulating antioxidant enzymes, thereby interrupting the AKI-to-CKD transition.

Diabetic Nephropathy Models

Streptozotocin-induced diabetic nephropathy models provide strong evidence for the renoprotective potential of green-extracted phytochemicals. Polyphenol-rich extracts improve glycemic control, reduce albuminuria, and attenuate mesangial expansion and glomerulosclerosis.

Mechanistically, these effects are mediated through inhibition of advanced glycation end-products (AGEs), suppression of TGF-β/Smad signaling, and enhancement of endothelial nitric oxide bioavailability. Notably, extracts produced using eco-friendly techniques demonstrate higher consistency in reducing oxidative and inflammatory markers across studies.

Hypertensive and Fibrotic Models

In models of hypertension-induced renal injury and unilateral ureteral obstruction, green-extracted phytochemicals reduce interstitial fibrosis and collagen deposition. Anti-fibrotic efficacy is strongly associated with inhibition of EMT and downregulation of α-smooth muscle actin and fibronectin expression.

These findings confirm that nephroprotection is not limited to antioxidant activity alone but extends to structural preservation of renal parenchyma.

Pharmacokinetics and Bioavailability Advantages

One of the major barriers to clinical translation of phytochemicals is poor oral bioavailability. Green extraction technologies partially overcome this limitation by producing extracts with optimized particle size, improved solubility, and enhanced stability.

Supercritical fluid extraction yields lipophilic fractions with superior intestinal absorption, while ultrasound-assisted extraction enhances release of glycosylated polyphenols that undergo favorable gut metabolism. Improved pharmacokinetic profiles translate into lower effective doses and reduced inter-individual variability, an important consideration for CKD patients with altered drug metabolism and excretion.

Clinical Evidence and Human Trials

Early-Phase and Pilot Clinical Studies

Several small-scale clinical studies and randomized controlled trials have evaluated phytochemicals such as curcumin, resveratrol, green tea catechins, and quercetin in CKD patients. Outcomes consistently show reductions in inflammatory markers (CRP,

IL-6), oxidative stress indices, and, in some cases, modest improvements in estimated glomerular filtration rate (eGFR).
Green-extracted formulations demonstrate improved tolerability and fewer gastrointestinal adverse effects, likely due to reduced solvent residues and lower required dosages. Importantly, no significant nephrotoxicity has been reported in these studies, supporting long-term safety.

Adjunctive Therapy in Dialysis Patients
In hemodialysis and peritoneal dialysis patients, phytochemical supplementation has been explored as an adjunct therapy to reduce systemic inflammation and oxidative burden. Polyphenol-rich extracts reduce lipid peroxidation, improve endothelial function, and may contribute to better cardiovascular outcomes—an essential consideration given the high cardiovascular mortality in CKD.
Green extraction enhances clinical acceptability by ensuring batch-to-batch consistency and compliance with regulatory safety standards.

Safety, Toxicity, and Regulatory Considerations
Toxicological studies consistently indicate a wide safety margin for nephroprotective phytochemicals when administered at therapeutic doses. Green extraction methods further reduce toxicity risks by eliminating residual organic solvents and minimizing formation of degradation products.
However, variability in plant source, extraction parameters, and formulation still presents challenges. Regulatory approval requires standardized extraction protocols, validated quality control markers, and rigorous clinical trial designs. Green technologies are increasingly favored by regulatory agencies due to their environmental sustainability and reproducibility.

Limitations of Current Evidence
Despite promising data, several limitations must be acknowledged:
Small sample sizes in clinical trials limit statistical power.
Heterogeneity in CKD etiology complicates outcome interpretation.
Short intervention durations may underestimate long-term benefits.
Lack of head-to-head comparisons between green-extracted and conventional extracts in humans.
Addressing these gaps requires multicenter randomized trials with standardized formulations and clinically meaningful endpoints.

Translational Potential and Future Directions
The convergence of mechanistic evidence, preclinical efficacy, and early clinical success positions green-extracted phytochemicals as strong candidates for integrative nephroprotective therapy. Their multi-target actions align well with the complex pathophysiology of CKD, while green technologies enhance safety, sustainability, and regulatory feasibility.
Future research should prioritize:
Dose-response and pharmacokinetic optimization
Combination therapies with standard nephroprotective drugs
Biomarker-guided patient stratification
Long-term outcome-based clinical trials

Challenges, Future Perspectives, and Conclusion

Current Challenges in Translating Green-Extracted Phytochemicals to CKD Therapy

Despite compelling experimental and emerging clinical evidence, several scientific, technical, and regulatory challenges hinder the full integration of green-extracted phytochemicals into routine management of Chronic Kidney Disease (CKD).

One of the primary challenges is **standardization**. Phytochemical composition varies significantly with plant species, geographical origin, harvesting season, and extraction parameters. Even within green extraction frameworks, differences in ultrasound frequency, microwave power, pressure, temperature, and solvent composition can markedly influence extract profiles. This variability complicates reproducibility, dose optimization, and cross-study comparisons.

Another major limitation is the **lack of large-scale, long-term randomized clinical trials.** Most available human studies involve small sample sizes, short intervention periods, and surrogate endpoints such as inflammatory or oxidative stress markers rather than hard renal outcomes (eGFR decline, dialysis initiation, or mortality). Moreover, CKD is a heterogeneous condition with diverse etiologies, including diabetes, hypertension, glomerulopathies, and genetic disorders, making uniform therapeutic evaluation challenging.

Pharmacokinetic complexity also poses a barrier. Many nephroprotective phytochemicals exhibit limited oral bioavailability, extensive first-pass metabolism, and altered distribution in CKD patients due to impaired renal clearance and uremic toxin accumulation. Although green extraction improves phytochemical integrity and solubility, formulation strategies such as nanoencapsulation, solid dispersions, or phytosome complexes are often required to achieve clinically relevant exposure.

From a regulatory perspective, **classification ambiguity** remains problematic. Herbal extracts may be regulated as foods, nutraceuticals, or drugs depending on jurisdiction, resulting in inconsistent quality requirements and approval pathways. While green extraction aligns well with modern regulatory expectations regarding sustainability and safety, harmonized guidelines for phytopharmaceuticals in nephrology are still lacking.

Future Perspectives and Research Directions

The future of nephroprotective phytotherapy lies in the **integration of green extraction, pharmacognostic rigor, and systems-level pharmacology.**

First, **standardized green extraction protocols** must be established for key nephroprotective plants and phytochemicals. This includes defining optimal extraction parameters, marker compounds, and fingerprinting techniques (HPLC, LC–MS, NMR) to ensure batch-to-batch consistency. Such standardization is essential for regulatory acceptance and multicenter clinical trials.

Second, **mechanism-driven research** should move beyond general antioxidant claims toward precise molecular targets. Emerging evidence suggests that phytochemicals modulate pathways such as Nrf2–Keap1, NF-κB, TGF-β/Smad, AMPK–SIRT1, and gut–kidney axis signaling. Integrating omics approaches (transcriptomics, metabolomics, and microbiomics) will enable identification of responder phenotypes and biomarkers for personalized phytotherapy in CKD.

Third, **advanced drug delivery systems** should be combined with green-extracted phytochemicals to overcome bioavailability limitations. Nanoformulations derived from biodegradable, plant-compatible materials can further enhance renal targeting, reduce dosing frequency, and improve patient adherence—critical factors in chronic disease management.

Fourth, **well-designed clinical trials** are urgently needed. Future studies should:

Include adequate sample sizes and longer follow-up

Stratify patients by CKD stage and etiology
Compare green-extracted formulations with both placebo and conventional extracts
Evaluate clinically meaningful renal and cardiovascular endpoints
Additionally, exploring phytochemicals as **adjuncts to standard nephroprotective drugs** (e.g., RAAS inhibitors, SGLT2 inhibitors) may reveal synergistic benefits and reduce drug-related adverse effects.

Sustainability and Societal Impact

Green extraction technologies contribute not only to therapeutic innovation but also to **environmental sustainability.** Reduced solvent use, lower energy consumption, and minimal waste generation align with global goals for sustainable pharmaceutical development. For low- and middle-income countries, where CKD burden is rising rapidly and access to renal replacement therapy is limited, plant-based nephroprotective agents produced through green technologies offer a cost-effective and culturally acceptable option.

Conclusion

This review highlights the growing scientific evidence supporting green-extracted nephroprotective phytochemicals as promising candidates for the management of chronic kidney disease. By integrating pharmacognostic validation, sustainable extraction technologies, and mechanistic pharmacological insights, green extraction offers a transformative approach to herbal drug development.

Preclinical studies consistently demonstrate antioxidant, anti-inflammatory, anti-fibrotic, and metabolic regulatory effects, while early clinical data suggest favorable safety and therapeutic potential. Although significant challenges remain—particularly regarding standardization, bioavailability, and large-scale clinical validation—the convergence of green chemistry and renal pharmacology provides a strong foundation for future translational success.

In conclusion, green extraction of nephroprotective phytochemicals represents a scientifically sound, environmentally responsible, and clinically promising strategy that may complement existing therapies and contribute meaningfully to slowing CKD progression in the years ahead.

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