

Journal of Molecular Science

www.jmolecularsci.com

ISSN:1000-9035

Nephroprotective Potentials of Plant-Derived Phytochemicals: Evidence from Experimental Rat Models

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Article Information

Received: 22-08-2025

Revised: 17-09-2025

Accepted: 25-10-2025

Published: 19-11-2025

Keywords

*Phytochemicals,
Nephroprotection, Rat models,
Oxidative stress, Inflammation
· Cisplatin nephrotoxicity,
Antioxidant mechanisms*

ABSTRACT

Kidney diseases are a major public health issue worldwide and are commonly caused by exposure to nephrotoxic drugs, environmental poisons, metabolic disturbances, or reactive oxygen species (ROS). **Phytochemicals and Renal Injury:** Many pre-clinical studies in rats have generated and validated useful mechanistic insights into the protection afforded by phytochemicals. Various plant-based compounds, including flavonoids, phenolic acids, alkaloids, terpenoids, saponins, and lignans, have pronounced antioxidant, anti-inflammatory, and anti-apoptotic capacities, resulting in protection against structural and functional kidney impairment. Experimental studies on gentamicin-, cisplatin-, and adenine- induced nephrotoxicity have presented evidence that these phytochemicals regulate several pathways such as Nrf2/ARE, NF- κ B, TGF- β , and MAPK. Additionally, the nephroprotective potential of these compounds has been enhanced through bioavailability modifications such as nanoformulation and use in combination therapy. In this review, we systematically provide the mechanisms of action, experimental evidence, and translational capacities driving plant phytochemicals as nephroprotective agents in rat models of nephropathy, and their roles in providing safer and more effective drinks for nephroprotection.

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INTRODUCTION:

Kidney diseases continue to be a major public health problem around the world, and their prevalence is increasing due to diabetes, high blood pressure, environmental toxins, and diseases related to unhealthy lifestyles. The kidney is more susceptible to oxidative stress, inflammation, and structural damage on account of its high metabolic activity and relatively twisted vascular architecture [1]. Therefore, more and more attention is being

paid to screening for safe and effective drugs that may contribute to the therapeutic approach of repairing kidney injury in different stages. Phytochemicals derived from plants have shown potential as nephroprotective agents, particularly in preclinical rat models that provide a comprehensive analysis of their biochemical and histological benefits. These bioactive substances are full of antioxidants, anti-inflammatory agents, and anti-fibrotic agents [2,3]. They are a complete way to keep the kidneys working well and stop kidney disease from becoming worse. Millions of individuals all over the globe have kidney difficulties that last a long time or come on suddenly. The number of people with these problems is expanding since people are becoming older and more people are having metabolic disorders. Chronic kidney disease (CKD) is a significant non-communicable illness that kills a lot of people, makes life less enjoyable, and costs a lot of money to treat [4]. A lot of regions, notably low- and middle-income nations, have an even worse

issue since they don't have adequate early diagnostic tools or access to renal replacement medicines. Environmental contaminants, nephrotoxic drugs, and what we eat all make kidney problems more common. Many instances of kidney disease don't get detected until the condition has grown worse, since early damage doesn't always show any signs. That underscores the importance of having therapies that shield the kidneys and that stop problems from happening [5].

Phytochemicals are active substances of medicinal plants. They have garnered a lot of attention since they are great at protecting the kidneys. Some of the substances that have high antioxidant and anti-inflammatory actions that fight against the primary causes of kidney injury include flavonoids, terpenoids, alkaloids, phenolic acids, and saponins [6]. Studies on rats have demonstrated that diverse plant extracts and isolated phytochemicals may lessen oxidative stress, enhance kidney function, stabilize cell membranes, and restore normal histological structure. They are attractive candidates for nephroprotection because they may affect numerous molecular pathways at once. Phytochemicals also often have good safety profiles, are cost-effective, and are accepted by many cultures. This makes them possible therapeutic options or additions to standard therapies for preventing kidney injury [7,8]. ACE inhibitors, angiotensin receptor blockers, diuretics, and antioxidants are some of the medications that may aid with renal disorders. But these treatments only protect you somewhat and have a lot of adverse effects [9]. Many synthetic medications do not do a good job of reducing oxidative stress, inflammation, or fibrosis, which are all important ways that kidney damage occurs [10][11,12]. In addition, prolonged administration of certain drugs may contribute to the aggravation of renal insufficiency or the development of systemic toxic symptoms. The limited effectiveness of standard treatment in halting disease progression underscores the need for novel nephroprotective approaches that are both secure and comprehensive. This has sparked scientific interest in natural substances that may modify numerous disease processes linked to kidney damage.

Experimental Rat Models of Nephropathy: Cisplatin-Induced Nephrotoxicity:

Cisplatin is often used in rat research to replicate acute kidney damage owing to its preferential accumulation in renal tubular cells. It produces oxidative stress, inflammation, and apoptosis, which raises the amounts of creatinine and urea in the blood, damages the tubules, and weakens the body's defenses against free radicals. This model is useful for the assessment of phytochemicals that

protect cells and scavenge free radicals [13].

Gentamicin-induced nephropathy

Gentamicin damages the kidneys by producing reactive oxygen species and disrupting the function of lysosomes and mitochondria. Damage tends to be dose-dependent. It causes proximal tubule damage, increases oxidative markers, and disturbs ionic balance [14]. This model enables us to evaluate the degree to which plant chemicals protect the kidneys' function by stabilizing membranes and reducing oxidative damage [15].

Adenine and Streptozotocin-Induced Chronic Renal Injury

Donating adenine causes crystals to accumulate and fibrosis to develop among the cells, a hallmark of chronic kidney disease. Streptozotocin (STZ) is a hyperglycemic agent that causes diabetic nephropathy, characterized by glomerulosclerosis, proteinuria, and inflammation. These long-term models are useful for testing phytochemicals that might exert inflammatory, fibrotic, and metabolic effects over time [16].

Ischemia-Reperfusion and Oxidative Stress Models

Ischemia reperfusion damage (IRI) in the kidney is caused by a period of time when blood is stopped to the kidneys, which leads to hypoxia and an oxidative burst at the moment when blood flow returns [17]. It's bad for the tubes, causes inflammation, and screws with the mitochondria. People also use oxidative stress-producing agents such as hydrogen peroxide or ferric nitrilotriacetate. These models assist researchers in finding plant antioxidants that could prevent acute oxidative damage to the kidneys [18].

Relevance and Translational Aspects of Rat Models

Rat models closely mimic key molecular and histological aspects of human kidney diseases, and are therefore suitable for preclinical trials on botanical nephroprotectants. They help with causing controlled injuries, repeating them and testing biomarkers [19]. Although there is variability between animals, much of the results from these models draw parallels with humans. Which means that they can be used in the design of new effective drugs [20].

Major Classes of Plant-Derived Phytochemicals with Nephroprotective Activity

Quercetin, kaempferol, catechin, and rutin are all flavonoids that are strong antioxidants and anti-inflammatories. They inhibit tubular degradation and reduce high levels of renal biomarkers. Phenolic acids, including gallic, caffeic, and ferulic

acid, enhance antioxidant defenses, diminish lipid peroxidation, and preserve normal renal histology in chemically induced nephropathy [21,22]. Alkaloids like berberine, colchicine, and piperine protect the kidneys in several ways, including by making mitochondria more stable, stopping pro-inflammatory mediators, and lowering fibrosis. Terpenoids and saponins, such as ursolic acid, ginsenosides, and glycyrrhizin, have considerable cytoprotective properties by modulating immunological responses, preventing apoptosis, and promoting cellular regeneration, particularly in ischemia–reperfusion and oxidative stress models [23]. Lignans and tannins, such as silymarin,

ellagic acid, and proanthocyanidins, assist in preserving the kidneys by being potent antioxidants, increasing microvascular function, and halting protein oxidation. These groupings of phytochemicals operate together via pathways that are linked to one another to protect the structure and function of the kidneys. This shows how helpful they might be in treating nephropathy [24]. An overview of the primary plant-based phytochemical kinds, their roles in kidney protection, and the outcomes of studies using rats with renal injury is presented in table 1.

Table 1 An overview of the primary plant-based phytochemical kinds, their roles in kidney protection, and the outcomes of studies using rats with renal injury

Phytochemical Class	Representative Compounds	Primary Nephroprotective Mechanisms	Key Outcomes Observed in Rat Models	References
Flavonoids	Quercetin, Kaempferol, Catechin, Rutin	Potent antioxidant activity, free radical scavenging, inhibition of inflammatory cytokines (TNF- α , IL-6), regulation of apoptotic pathways	Reduction in serum creatinine and urea, improved GSH and SOD levels, decreased tubular necrosis, protection against cisplatin and gentamicin toxicity	[25–27]
Phenolic Acids	Gallic acid, Caffeic acid, Ferulic acid	Enhancement of endogenous antioxidant enzymes, suppression of nitric oxide overproduction, inhibition of lipid peroxidation	Restoration of renal histoarchitecture, reduction of oxidative biomarkers (MDA), protection in drug- and toxin-induced nephropathy	[28–30]
Alkaloids	Berberine, Colchicine, Piperine	Anti-inflammatory and anti-fibrotic effects, mitochondrial protection, modulation of glucose and lipid metabolism	Improved renal function markers, prevention of glomerular and tubular damage, attenuation of diabetic and chronic renal injuries	[31,32]
Terpenoids & Saponins	Ursolic acid, Ginsenosides, Glycyrrhizin	Anti-apoptotic effects, immune modulation, inhibition of fibrosis, membrane stabilization	Reduced inflammatory infiltration, improved renal regeneration, protection from ischemia–reperfusion injury and oxidative stress	[33,34]
Lignans & Tannins	Silymarin, Ellagic acid, Proanthocyanidins	Strong antioxidant potential, enhancement of microcirculation, inhibition of protein oxidation and fibrosis	Decreased oxidative stress markers, preservation of glomerular structure, protection against toxin-induced and chronic renal damage	[35,36]

Mechanistic Insights into Nephroprotective Action

Antioxidant and free radical scavenging mechanisms

Many plant phytochemicals protect kidney tissues by neutralizing reactive oxygen species (ROS) and making the body's natural antioxidant defenses stronger [37]. They reduce levels of lipid peroxidation indicators such as malondialdehyde (MDA) and boost levels of glutathione (GSH), superoxide dismutase (SOD), and catalase. These substances restore redox equilibrium, which stops oxidative damage to glomeruli and renal tubules. This is an important occurrence in most kinds of nephropathy [38].

Anti-inflammatory and cytokine modulation

Phytochemicals significantly suppress renal

inflammation by downregulating pro-inflammatory cytokines, including TNF- α , IL-1 β , and IL-6. They also block inflammatory mediators like COX-2 and iNOS from being turned on, which stops immune cells from getting into tissues. This leads to less interstitial edema, a lower oxidative burst, and the preservation of renal architecture in experimental models [39,40].

Inhibition of Apoptosis and Mitochondrial Protection

Many bioactive plant substances prevent renal cell death by stabilizing mitochondrial membranes and altering apoptotic proteins [41]. They raise the levels of anti-apoptotic proteins like Bcl-2 and reduce the levels of pro-apoptotic proteins like Bax and caspase-3. Phytochemicals assist the kidneys' work by keeping mitochondria healthy and making

ATP. They also prevent tubular cells from dying [42,43].

Regulation of Key Molecular Pathways (Nrf2/ARE, NF- κ B, TGF- β , MAPK)

Phytochemicals influence several signaling pathways associated with renal injury and regeneration. When the Nrf2/ARE pathway is switched on, it makes antioxidant genes work harder, which helps cells deal with oxidative stress. Stopping NF- κ B signaling prevents inflammation, and altering TGF- β lowers fibrosis and the development of the extracellular matrix [44]. Controlling MAPK pathways also helps keep oxidative damage, apoptosis, and inflammation in check. These acts that affect more than one item highlight how useful plant chemicals may be as medications (Figure 1).

Role in Improving Renal Hemodynamics and Tubular Function

Some phytochemicals make the endothelium work better and minimize oxidative damage to blood vessels, which promotes blood flow to the kidneys and glomerular filtration [45]. They assist the body in reabsorbing electrolytes, stabilize tubular membranes, and make nitric oxide more accessible. Improved hemodynamics and tubular integrity result in increased urine output, reduced proteinuria, and the reestablishment of normal renal physiology in nephrotoxic animals [46].

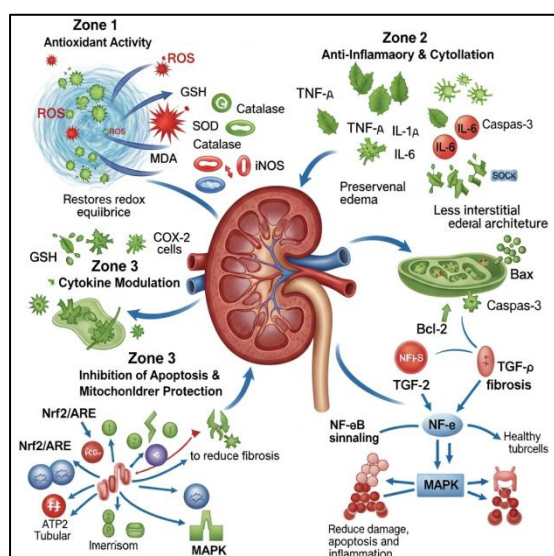


Figure 1 The graphic illustrates the primary mechanisms by which phytochemicals safeguard renal tissues in experimental animals.

In Figure 1, Zone 1 focuses on antioxidant activities, such as getting rid of reactive oxygen species (ROS), boosting the body's own antioxidants (GSH, SOD, and catalase), and lowering lipid peroxidation (MDA). Zone 2 has anti-inflammatory and cytoprotective properties by

reducing inflammatory cytokines (TNF- α , IL-1 β , IL-6), diminishing edema, and enhancing the architecture of the interstitial space. Zone 3 illustrates how Bax, Bcl-2, and caspase-3 interact to prevent cells from dying and mitochondria from becoming unhealthy. Phytochemicals also modulate the major signalling pathways, including Nrf2/ARE, NF- κ B, TGF- β , and MAPK. All of these mechanisms work in concert in order to reduce oxidative stress, inflammation, fibrosis, and damage of the tubules; these features are necessary to keep the kidneys healthy [47].

Experimental Evidence from Rat Models

Phytochemicals in Cisplatin-Induced Nephrotoxicity

Plant bioactive substances have long been used to protect rats against cisplatin-induced acute kidney injury. Typical experimental findings encompass abrogating near alterations in cisplatin-induced serum creatinine and blood urea nitrogen (BUN) elevations, decreasing lipid peroxidation markers [malondialdehyde (MDA)], and enhancing endogenous antioxidant defense system (GSH, SOD, catalase) levels of hepatic tissue data mass [48]. Histologically, treated animals demonstrate reduced tubular necrosis, less cast formation, and preservation of brush border integrity relative to untreated controls. The advantages stem from robust antioxidant properties, inhibition of inflammatory cytokines, stabilization of mitochondrial function, and cessation of apoptotic signals [49].

Phytochemicals in Gentamicin-Induced Nephropathy

In gentamicin nephrotoxicity models, phytochemicals mitigate the drug's nephrotoxic cascade by reducing oxidative stress, slowing membrane lipid peroxidation, and lowering inflammatory cell infiltration [50]. In experimental conditions, rats with phytochemical therapy exhibit improved renal function tests (lowered blood creatinine and BUN), stabilized electrolyte concentrations, and decreased markers of oxidative damage [51]. Histopathology usually shows less degeneration of the proximal tubules, less vacuolation, and less inflammation in the interstitial space. A lot of therapies also safeguard the ultrastructure of mitochondria and lessen the chance of lysosomal rupture, which are two critical things that happen when aminoglycosides injure cells [52].

Phytochemicals in Diabetic and Adenine-Induced Renal Injury

In streptozotocin (STZ)-induced diabetic nephropathy, phytochemicals improve glucose control or reduce eventual kidney damage via anti-

inflammatory, anti-fibrotic, and antioxidant pathways. Results often indicate reduced proteinuria, decreased serum creatinine levels, and diminished glomerulosclerosis indices [53]. In adenine-induced chronic kidney disease models, phytochemicals reduce crystal deposition, interstitial fibrosis, and tubular atrophy, as seen by improved renal function indicators and lower levels of fibrosis-related markers (e.g., collagen, TGF- β). Long-term administration in these animals demonstrates a reduction in the progression of structural damage and an improvement in indicators of renal remodeling [54].

Comparative Outcomes and Histopathological Evidence

Common experimental end points among models emphasize nephroprotective action of phytochemicals: (1) biochemistry improvement downregulated serum creatinine/Urea and uremic markers; (2) ameliorative effects of oxidative stress decrease MDA levels/upregulate SOD/GSH/catalase activities; (3) suppress pro-inflammatory mediators decline TNF- α /IL-1 β /IL-6 and reduced immune cell adhesion, migration, and accumulation at injury site; (4) maintenance of tissue integrity decreased tubular necrosis/glomerular damage/interstitial fibrosis [55]. Histopathological scoring repeatedly shows lower grades of damage in the treated animals with better tubular architecture, less cast formation, and decreased fibrotic staining. The degree of protection is dependent on the compound, dose, and timing; however, the commonality between cisplatin, gentamicin, diabetic, and adenine models highlights the translational relevance of phytochemical intervention(s) as an adjunctive regimen for preventing/reversing nephropathy [56].

Pharmacokinetic and Bioavailability Challenges Limitations of Natural Phytochemicals In Vivo

Many phytochemicals possess strong nephroprotective effects in preclinical studies, but their therapeutic value is hampered by poor pharmacokinetics. Lest we become too discouraged, there are natural substances that do not easily dissolve in water, that degrade quickly, that do not cross membranes very efficiently, and finally are poorly absorbed by the body [57]. That is, these compounds are resistant to uptake by renal tissues and exist in the tissues. A short plasma half-life and first-pass metabolism also result in shorter therapeutic effects, indicating that higher amounts or more frequent doses are necessary [58].

Nanoformulation-Based Delivery Systems

Nanodelivery systems offer a huge potential for overcoming the bioavailability issue of phytochemicals. Nanoparticles, liposomes,

polymeric micelles, solid lipid nanoparticles, and nanoemulsions aid in solubilizing the substance and inhibit enzymes from breaking it down, making it easier for the kidneys to locate it [59]. They allow drugs to be released in a controlled manner, remain within the body for longer periods, and be more readily taken up by cells. In models of rat nephropathy, it has been demonstrated that flavonoids, phenolics, and alkaloids in nanoformulation are highly potent antioxidant/anti-inflammatory agents when compared with their unformulated counterparts, suggesting higher therapeutic efficiency [60].

Combination Therapy Approaches for Enhanced Nephroprotection

These combinations are superior to monotherapy, making it more efficient for the antioxidants, inhibition of multiple inflammatory pathways, and fibrosis. Co-administration strategies might further improve pharmacokinetics by decreasing metabolism or increasing cellular uptake. Combination therapy can be especially beneficial in challenging kidney diseases, including diabetic nephropathy, when it is necessary to not only protect the body against more than one target [61].

Safety Profile and Toxicological Considerations

Dose-Dependent Effects and Toxicity Markers

Oxidative disequilibrium, liver injury, or metabolic enzyme problems can be generated at high doses. In rats, toxicity symptoms of increased serum liver and renal indices (ALT, AST), creatinine, BUN blood parameters, as well as induction of oxidative stress markers such as MDA and reduction in GSH levels were reported. Histopathologic signs, such as tubular degeneration and inflammatory infiltration or glomerular damage, act as an early sign of dose-dependent toxicity [62].

Safety Evaluation in Experimental Rat Studies

Preclinical testing meticulously assesses the safety of phytochemicals through acute, sub-acute, and chronic toxicity studies. Most of the nephroprotective phytochemicals have abundant safety margins; this means they do not produce very serious damage at therapeutic doses [63]. Histological analysis of the liver, kidney, and other organs does not reveal any pathological abnormalities. This indicates that the compounds are appropriate for further investigations; however, interspecies differences should be taken into account in extrapolation to humans [64–66].

Future Directions in Toxicity Prediction

Computational toxicology and In Silico behaviour are improving, so we can predict how safe phytochemicals are before we test them on live organisms. Such approaches, when combined with omics technology and high-throughput screening,

may help to find safe dosages more rapidly and curtail the amount of animal testing that needs to be conducted [67]. Future studies should emphasize the incorporation of conventional toxicology in line with state-of-the-art prediction platforms to secure safer and effective candidate nephroprotective drugs [68].

Translational Relevance and Future Prospects Bridging Preclinical Findings with Clinical Nephropathy

Rat experiments have shown that due to values, phytochemicals can attenuate oxidative stress, inflammation, and fibrosis -all mechanisms of human nephropathy [69]. These are promising results, but need to be tested more rigorously through pharmacokinetic analyses, safety assessment, and controlled clinical tests before they can be fully exploited. We need to know the distinctions across animals and how to effectively dose them to apply this to people [70,71].

Potential for Phytochemical-Based Drug Development

Phytochemicals are attractive candidates for generating novel nephroprotective medicines or adjuvant therapy since they can target multiple things at once. You can modify them to make them more stable, soluble, and better at targeting tissues since they have different structures [72]. New formulation technologies, including nano-delivery systems, make them even better for treating disorders and make it possible to employ phytochemicals in clinical settings [73].

Integration with Personalized and Preventive Nephrology

Phytochemicals are very promising for customized therapy since they are safe and can affect various pathways that lead to renal issues [74]. Adding these medicines to preventative regimens may reduce the disease's development, particularly for persons with diabetes, high blood pressure, or drug-induced nephrotoxicity who are at high risk. In the future, techniques may combine phytochemicals with genetic and metabolic analysis to make treatments unique to each patient [75].

CONCLUSION:

Plant phytochemicals are a potential category of nephroprotective compounds that may impact many molecular pathways that contribute to kidney injury. Evidence from various experimental rat models, including cisplatin, gentamicin, diabetic-, and adenine-induced nephropathy, consistently demonstrates their capacity to mitigate oxidative stress, suppress inflammation, inhibit apoptosis, and modulate critical signaling pathways such as Nrf2/ARE, NF- κ B, TGF- β , and MAPK. Major

groups of phytochemicals, including flavonoids, phenolic acids, alkaloids, terpenoids, saponins, lignans, and tannins, have been shown to have significant renoprotective effects via biochemical restoration and histopathological enhancement. Even though these phytochemicals are good for you, it's tricky to employ them in clinical settings since they don't dissolve well, are broken down quickly, and don't work well in the body. Novel nanoformulation approaches and combined treatment strategies could help to maximize their therapeutic efficacy. Moreover, preclinical results from safety assessments on animal models suggest that most phytochemicals exhibit desirable toxicity patterns at well tolerated doses. In the future, well-designed clinical trials and predictive toxicological technologies will be needed to tailor phytochemicals into nephrology preventive medicine. This will be important, for these drugs to work well with phytochemicals. The growing body of experimental data indicates that phytochemicals hold great promise as safe, easily available and multitargeted therapies for kidney diseases and a mean for preventing their progression.

REFERENCES:

1. Francis A, Harhay MN, Ong ACM, Tummalapalli SL, Ortiz A, Fogo AB, et al. Chronic kidney disease and the global public health agenda: an international consensus. *Nature Reviews Nephrology* 2024 20:7 2024;20:473–85. <https://doi.org/10.1038/s41581-024-00820-6>.
2. Aware CB, Patil DN, Suryawanshi SS, Mali PR, Rane MR, Gurav RG, et al. Natural bioactive products as promising therapeutics: A review of natural product-based drug development. *South African Journal of Botany* 2022;151:512–28. <https://doi.org/10.1016/J.SAJB.2022.05.028>.
3. Screening: Learn More – Advantages and disadvantages of screening tests 2025.
4. Mark PB, Stafford LK, Grams ME, Aalruz H, ElHafeez SA, Abdelgalil AA, et al. Global, regional, and national burden of chronic kidney disease in adults, 1990–2023, and its attributable risk factors: a systematic analysis for the Global Burden of Disease Study 2023. *The Lancet* 2025;0. [https://doi.org/10.1016/S0140-6736\(25\)01853-7](https://doi.org/10.1016/S0140-6736(25)01853-7).
5. Moyazzem Hossain M, Abdulla F, Rahman A. Challenges and difficulties faced in low- and middle-income countries during COVID-19. *Health Policy Open* 2022;3:100082. <https://doi.org/10.1016/J.HPOPEN.2022.100082>.
6. Kumar A, Nirmal P, Kumar M, Jose A, Tomer V, Oz E, et al. Major Phytochemicals: Recent Advances in Health Benefits and Extraction Method. *Molecules* 2023;28:887. <https://doi.org/10.3390/MOLECULES28020887>.
7. Milad SS, Elshoky HA, Ali SE, Khattab MS, Attia MZ, Azouz AM. Nanoparticle delivery of combined plant extracts enhances immune response in immunocompromised rats. *Scientific Reports* 2025 15:1 2025;15:39015-. <https://doi.org/10.1038/s41598-025-21329-3>.
8. Zouine N, Ghachtouli N El, Abed S El, Koraichi SI. A comprehensive review on medicinal plant extracts as antibacterial agents: Factors, mechanism insights and future prospects. *Sci Afr* 2024;26:e02395. <https://doi.org/10.1016/J.SCIAF.2024.E02395>.
9. Sica DA. Combination ACE Inhibitor and Angiotensin Receptor Blocker Therapy—Future Considerations. *The Journal of Clinical Hypertension* 2007;9:78. <https://doi.org/10.1111/J.1524-6175.2007.6359.X>.

10. Ahmad H, Khan H, Haque S, Ahmad S, Srivastava N, Khan A. Angiotensin-Converting Enzyme and Hypertension: A Systemic Analysis of Various ACE Inhibitors, Their Side Effects, and Bioactive Peptides as a Putative Therapy for Hypertension. *J Renin Angiotensin Aldosterone Syst* 2023;2023:7890188. <https://doi.org/10.1155/2023/7890188>.
11. Antognini N, Portman R, Dong V, Webb NJ, Chand DH. Detection, Monitoring, and Mitigation of Drug-Induced Nephrotoxicity: A Pragmatic Approach. *Ther Innov Regul Sci* 2023;58:286. <https://doi.org/10.1007/S43441-023-00599-X>.
12. Unwin RJ. Toxic nephropathy: Adverse renal effects caused by drugs. *Eur J Intern Med* 2022;96:20–5. <https://doi.org/10.1016/J.EJIM.2021.09.008>.
13. Perše M, Večerić-Haler Ž. Cisplatin-Induced Rodent Model of Kidney Injury: Characteristics and Challenges. *Biomed Res Int* 2018;2018:1462802. <https://doi.org/10.1155/2018/1462802>.
14. Cumaoglu MO, Makav M, Dag S, Uysal AY, Baser L, LeBaron TW, et al. Combating oxidative stress and inflammation in gentamicin-induced nephrotoxicity using hydrogen-rich water. *Tissue Cell* 2024;91:102604. <https://doi.org/10.1016/J.TICE.2024.102604>.
15. Zhang M, Zhou Y, Wang X, Li Y, Wu X. Gentamicin aggravates renal injury by affecting mitochondrial dynamics, altering renal transporters expression, and exacerbating apoptosis. *Toxicol Lett* 2025;412:55–67. <https://doi.org/10.1016/j.toxlet.2025.07.1418>.
16. Yang Q, Su S, Luo N, Cao G. Adenine-induced animal model of chronic kidney disease: current applications and future perspectives. *Ren Fail* 2024;46:2336128. <https://doi.org/10.1080/0886022X.2024.2336128>.
17. Malek M, Nematbakhsh M. Renal ischemia/reperfusion injury; from pathophysiology to treatment. *J Renal Inj Prev* 2015;4:20. <https://doi.org/10.12861/JRIP.2015.06>.
18. Zhang M, Liu Q, Meng H, Duan H, Liu X, Wu J, et al. Ischemia-reperfusion injury: molecular mechanisms and therapeutic targets. *Signal Transduction and Targeted Therapy* 2023 9:1 2024;9:12-. <https://doi.org/10.1038/s41392-023-01688-x>.
19. Szpirer C. Rat models of human diseases and related phenotypes: a systematic inventory of the causative genes. *Journal of Biomedical Science* 2020 27:1 2020;27:84-. <https://doi.org/10.1186/S12929-020-00673-8>.
20. Mullins LJ, Conway BR, Menzies RI, Denby L, Mullins JJ. Renal disease pathophysiology and treatment: contributions from the rat. *Dis Model Mech* 2016;9:1419. <https://doi.org/10.1242/DMM.027276>.
21. Jan R, Khan M, Asaf S, Lubna, Asif S, Kim KM. Bioactivity and Therapeutic Potential of Kaempferol and Quercetin: New Insights for Plant and Human Health. *Plants* 2022;11:2623. <https://doi.org/10.3390/PLANTS11192623>.
22. Varshney P, Chandra P. Preclinical Data Extrapolation to Clinical Reality: A Translational Approach. *Curr Drug Discov Technol* 2024;21. <https://doi.org/10.2174/0115701638302778240417045451>.
23. Letchuman S, Madhuranga HDT, Madhurangi BLNK, Premarathna AD, Saravanan M. Alkaloids unveiled: A comprehensive analysis of novel therapeutic properties, mechanisms, and plant-based innovations. *Intelligent Pharmacy* 2025;3:268–76. <https://doi.org/10.1016/J.IPHA.2024.09.007>.
24. Landete JM. Ellagitannins, ellagic acid and their derived metabolites: A review about source, metabolism, functions and health. *Food Research International* 2011;44:1150–60. <https://doi.org/10.1016/J.FOODRES.2011.04.027>.
25. Mohan A, Dummi Mahadevan G, Anand Iyer V, Mukherjee TK, Haribhai Patel V, Kumar R, et al. Dietary flavonoids in health and diseases: A concise review of their role in homeostasis and therapeutics. *Food Chem* 2025;487:144674. <https://doi.org/10.1016/J.FOODCHEM.2025.144674>.
26. Do Socorro Chagas MS, Behrens MD, Moragas-Tellis CJ, Penedo GXM, Silva AR, Gonçalves-De-Albuquerque CF. Flavonols and Flavones as Potential anti-Inflammatory, Antioxidant, and Antibacterial Compounds. *Oxid Med Cell Longev* 2022;2022:9966750. <https://doi.org/10.1155/2022/9966750>.
27. Al Hoque A, Begum S, Dutta D. Occurrence, Chemical Nature, and Medicinal Benefits of Flavonoids: Rutin, Kaempferol, Quercetin, Anthocyanidins, Catechins, and Flavones. *Dietary Supplements and Nutraceuticals* 2025:185–208. https://doi.org/10.1007/978-981-96-8622-3_5.
28. Tutun H, Yipel M. Phenolic acids as potent antioxidant agents. *Advancement of Phenolic Acids in Drug Discovery: Fundamentals and Applications* 2024:145–75. <https://doi.org/10.1016/B978-0-443-18538-0.00003-2>.
29. Manivel P, Chen X. Chlorogenic, Caffeic, and Ferulic Acids and Their Derivatives in Foods. *Handbook of Dietary Phytochemicals* 2020:1–31. https://doi.org/10.1007/978-981-13-1745-3_22-1.
30. Lima VN, Oliveira-Tintino CDM, Santos ES, Morais LP, Tintino SR, Freitas TS, et al. Antimicrobial and enhancement of the antibiotic activity by phenolic compounds: Gallic acid, caffeic acid and pyrogallol. *Microb Pathog* 2016;99:56–61. <https://doi.org/10.1016/j.micpath.2016.08.004>.
31. Chakraborty A, Paudel KR, Wang C, De Rubis G, Chellappan DK, Hansbro PM, et al. Anti-inflammatory and anti-fibrotic effects of berberine-loaded liquid crystalline nanoparticles. *EXCLI J* 2023;22:1104. <https://doi.org/10.17179/EXCLI2023-6467>.
32. Wang K, Yin J, Chen J, Ma J, Si H, Xia D. Inhibition of inflammation by berberine: Molecular mechanism and network pharmacology analysis. *Phytomedicine* 2024;128:155258. <https://doi.org/10.1016/J.PHYMED.2023.155258>.
33. Câmara JS, Perestrelo R, Ferreira R, Berenguer C V., Pereira JAM, Castilho PC. Plant-Derived Terpenoids: A Plethora of Bioactive Compounds with Several Health Functions and Industrial Applications—A Comprehensive Overview. *Molecules* 2024;29:3861. <https://doi.org/10.3390/MOLECULES29163861>.
34. Ge J, Liu Z, Zhong Z, Wang L, Zhuo X, Li J, et al. Natural terpenoids with anti-inflammatory activities: Potential leads for anti-inflammatory drug discovery. *Bioorg Chem* 2022;124:105817. <https://doi.org/10.1016/J.BIOORG.2022.105817>.
35. Rudrapal M, Khairnar SJ, Khan J, Dukhyil A Bin, Ansari MA, Alomary MN, et al. Dietary Polyphenols and Their Role in Oxidative Stress-Induced Human Diseases: Insights Into Protective Effects, Antioxidant Potentials and Mechanism(s) of Action. *Front Pharmacol* 2022;13:806470. <https://doi.org/10.3389/FPHAR.2022.806470>.
36. Oluwole O, Fernando WB, Lumanlan J, Ademuyiwa O, Jayasena V. Role of phenolic acid, tannins, stilbenes, lignans and flavonoids in human health – a review. *Int J Food Sci Technol* 2022;57:6326–35. <https://doi.org/10.1111/IJFS.15936>.
37. Basist P, Parveen B, Zahiruddin S, Gautam G, Parveen R, Khan MA, et al. Potential nephroprotective phytochemicals: Mechanism and future prospects. *J Ethnopharmacol* 2022;283:114743. <https://doi.org/10.1016/J.JEP.2021.114743>.
38. Ighodaro OM, Akinloye OA. First line defence antioxidants-superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPX): Their fundamental role in the entire antioxidant defence grid. *Alexandria Journal of Medicine* 2018;54:287–93. <https://doi.org/10.1016/J.AJME.2017.09.001>.
39. Josa E, Barril G, Ruperto M. Potential Effects of Bioactive Compounds of Plant-Based Foods and Medicinal Plants in Chronic Kidney Disease and Dialysis: A Systematic Review. *Nutrients* 2024, Vol 16, Page 4321 2024;16:4321.

- <https://doi.org/10.3390/NU16244321>.
40. Mandal S, Goswami RK, Mavi AK, Kumar S, Khangembam BK, Rizvi MA, et al. Anti-inflammatory phytochemicals: alleviating inflammation and immune responses. *Phytochemicals in Food for Health and Wellness* 2026;123–43. <https://doi.org/10.1016/B978-0-443-26494-8.00021-5>.
 41. Cecchini V, Troise D, Sabatino A, Cicirelli A, Hallergård G, Avesani CM, et al. Optimizing Mitochondrial Targeting with Bioactive Compounds: Dietary Pattern Considerations for Patients with Chronic Kidney Disease. *Journal of Renal Nutrition* 2025. <https://doi.org/10.1053/J.JRN.2025.08.002>.
 42. Cecchini V, Troise D, Sabatino A, Cicirelli A, Hallergård G, Avesani CM, et al. Optimizing Mitochondrial Targeting with Bioactive Compounds: Dietary Pattern Considerations for Patients with Chronic Kidney Disease. *Journal of Renal Nutrition* 2025. <https://doi.org/10.1053/J.JRN.2025.08.002>.
 43. Anchimowicz J, Zielonka P, Jakiela S. Plant Secondary Metabolites as Modulators of Mitochondrial Health: An Overview of Their Anti-Oxidant, Anti-Apoptotic, and Mitophagic Mechanisms. *Int J Mol Sci* 2025;26:380. <https://doi.org/10.3390/IJMS26010380/S1>.
 44. Ferrari E, Cord D, Rimbu MC, Iordache MP, Albulescu R, Pop S, et al. Phytochemicals as Epigenetic Modulators in Chronic Diseases: Molecular Mechanisms. *Molecules* 2025, Vol 30, Page 4317 2025;30:4317. <https://doi.org/10.3390/MOLECULES30214317>.
 45. Bujor A, Miron A, Trifan A, Luca SV, Gille E, Miron SD, et al. Phytochemicals and endothelial dysfunction: recent advances and perspectives. *Phytochemistry Reviews* 2020 20:4 2020;20:653–91. <https://doi.org/10.1007/S11101-020-09728-Y>.
 46. Alum EU. Role of phytochemicals in cardiovascular disease management: Insights into mechanisms, efficacy, and clinical application. *Phytomedicine Plus* 2025;5:100695. <https://doi.org/10.1016/J.PHYPLU.2024.100695>.
 47. Hunyadi A. The mechanism(s) of action of antioxidants: From scavenging reactive oxygen/nitrogen species to redox signaling and the generation of bioactive secondary metabolites. *Med Res Rev* 2019;39:2505–33. <https://doi.org/10.1002/MED.21592>;JOURNAL:JOURN L:10981128;WGROU:STRING:PUBLICATION.
 48. Zhou J, Nie RC, Yin YX, Cai XX, Xie D, Cai MY. Protective Effect of Natural Antioxidants on Reducing Cisplatin-Induced Nephrotoxicity. *Dis Markers* 2022;2022:1612348. <https://doi.org/10.1155/2022/1612348>.
 49. Huang H, Jin WW, Huang M, Ji H, Capen DE, Xia Y, et al. Gentamicin-Induced Acute Kidney Injury in an Animal Model Involves Programmed Necrosis of the Collecting Duct. *Journal of the American Society of Nephrology* 2020;31:2097–115. <https://doi.org/10.1681/ASN.2019020204/-/DCSUPPLEMENTAL>.
 50. Tomşa AM, Răchişan AL, Pandrea SL, Benea A, Uifălean A, Toma C, et al. Curcumin and Vitamin C Attenuate Gentamicin-Induced Nephrotoxicity by Modulating Distinctive Reactive Species. *Metabolites* 2022;13:49. <https://doi.org/10.3390/METABO13010049>.
 51. Cumaoglu MO, Makav M, Dag S, Uysal AY, Baser L, LeBaron TW, et al. Combating oxidative stress and inflammation in gentamicin-induced nephrotoxicity using hydrogen-rich water. *Tissue Cell* 2024;91:102604. <https://doi.org/10.1016/J.TICE.2024.102604>.
 52. Zollinger HU, Mihatsch MJ. Histopathology of the Renal Tubules. *Renal Pathology in Biopsy* 1978:118–38. https://doi.org/10.1007/978-3-642-66731-2_8.
 53. Situmorang PC, Zuhra CF, Lutfia A, Pasaribu KM, Hardiyanti R, Nugraha AP. Harnessing phytochemicals to combat diabetes: Insights into molecular pathways and therapeutic advances. *J Funct Foods* 2025;128:106799. <https://doi.org/10.1016/J.JFF.2025.106799>.
 54. Lopez-Giacoman S, Madero M. Biomarkers in chronic kidney disease, from kidney function to kidney damage. *World J Nephrol* 2015;4:57. <https://doi.org/10.5527/WJN.V4.I1.57>.
 55. Basist P, Parveen B, Zahiruddin S, Gautam G, Parveen R, Khan MA, et al. Potential nephroprotective phytochemicals: Mechanism and future prospects. *J Ethnopharmacol* 2022;283:114743. <https://doi.org/10.1016/J.JEP.2021.114743>.
 56. Gibson-Corley KN, Olivier AK, Meyerholz DK. Principles for valid histopathologic scoring in research. *Vet Pathol* 2013;50:10.1177/0300985813485099. <https://doi.org/10.1177/0300985813485099>.
 57. Basist P, Parveen B, Zahiruddin S, Gautam G, Parveen R, Khan MA, et al. Potential nephroprotective phytochemicals: Mechanism and future prospects. *J Ethnopharmacol* 2022;283. <https://doi.org/10.1016/j.jep.2021.114743>.
 58. Miners JO, Yang X, Knights KM, Zhang L. The Role of the Kidney in Drug Elimination: Transport, Metabolism, and the Impact of Kidney Disease on Drug Clearance. *Clin Pharmacol Ther* 2017;102:436–49. <https://doi.org/10.1002/CPT.757>.
 59. Manocha S, Dhiman S, Grewal AS, Guarve K. Nanotechnology: An approach to overcome bioavailability challenges of nutraceuticals. *J Drug Deliv Sci Technol* 2022;72:103418. <https://doi.org/10.1016/J.JDDST.2022.103418>.
 60. Adepu S, Ramakrishna S. Controlled Drug Delivery Systems: Current Status and Future Directions. *Molecules* 2021;26:5905. <https://doi.org/10.3390/MOLECULES26195905>.
 61. Li X, Peng X, Zoulikha M, Bofo GF, Magar KT, Ju Y, et al. Multifunctional nanoparticle-mediated combining therapy for human diseases. *Signal Transduction and Targeted Therapy* 2023 9:1 2024;9:1-. <https://doi.org/10.1038/s41392-023-01668-1>.
 62. Banerjee P, Gaddam N, Chandler V, Chakraborty S. Oxidative Stress-Induced Liver Damage and Remodeling of the Liver Vasculature. *Am J Pathol* 2023;193:1400–14. <https://doi.org/10.1016/J.AJP.2023.06.002>.
 63. Huang W, Percie du Sert N, Vollert J, Rice ASC. General Principles of Preclinical Study Design. *Handb Exp Pharmacol* 2020;257:55. https://doi.org/10.1007/164_2019_277.
 64. Mouleeswaran KS, Varghese J, Reddy MS. Atlas of Basic Liver Histology for Practicing Clinicians and Pathologists. *Atlas of Basic Liver Histology for Practicing Clinicians and Pathologists* 2023:1–116. <https://doi.org/10.1007/978-981-99-5762-0/COVER>.
 65. Gasmi B, Kleiner DE. Liver Histology Diagnostic and Prognostic Features. *Clin Liver Dis* 2019;24:61. <https://doi.org/10.1016/J.CLD.2019.09.004>.
 66. Cain OL, Hübscher SG. Histological assessment of the liver. *Medicine* 2019;47:707–12. <https://doi.org/10.1016/J.MPMED.2019.08.006>.
 67. Hernandez AF. In silico toxicology, a robust approach for decision-making in the context of next-generation risk assessment. *Toxicological Risk Assessment and Multi-System Health Impacts from Exposure* 2021:31–50. <https://doi.org/10.1016/B978-0-323-85215-9.00011-8>.
 68. Mugale MN, Dev K, More BS, Mishra VS, Washimkar KR, Singh K, et al. A Comprehensive Review on Preclinical Safety and Toxicity of Medicinal Plants. *Clinical Complementary Medicine and Pharmacology* 2024;4:100129. <https://doi.org/10.1016/J.CCMP.2024.100129>.
 69. Jing W, Xiaolan C, Yu C, Feng Q, Haifeng Y. Pharmacological effects and mechanisms of tannic acid. *Biomedicine & Pharmacotherapy* 2022;154:113561. <https://doi.org/10.1016/J.BIOPHA.2022.113561>.
 70. Zahra M, Abrahamse H, George BP. Flavonoids: Antioxidant Powerhouses and Their Role in

- Nanomedicine. Antioxidants 2024, Vol 13, Page 922
2024;13:922. <https://doi.org/10.3390/ANTIOX13080922>.
71. Basist P, Parveen B, Zahiruddin S, Gautam G, Parveen R, Khan MA, et al. Potential nephroprotective phytochemicals: Mechanism and future prospects. J Ethnopharmacol 2022;283:114743. <https://doi.org/10.1016/J.JEP.2021.114743>.
72. Basist P, Parveen B, Zahiruddin S, Gautam G, Parveen R, Khan MA, et al. Potential nephroprotective phytochemicals: Mechanism and future prospects. J Ethnopharmacol 2022;283:114743. <https://doi.org/10.1016/J.JEP.2021.114743>.
73. Kim HK, Kim SJ, Gil WJ, Yang CS. Exploring the therapeutic potential of phytochemicals: challenges and strategies for clinical translation. Phytomedicine 2025;145:157090. <https://doi.org/10.1016/J.PHYMED.2025.157090>.
74. Aljabali AAA, Obeid MA, Bashatwah RM, Qnais E, Gammoh O, Alqudah A, et al. Phytochemicals in Cancer Therapy: A Structured Review of Mechanisms, Challenges, and Progress in Personalized Treatment. Chem Biodivers 2025;22:e202402479. <https://doi.org/10.1002/CBDV.202402479>.