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Review Article

Anthraquinones in Kidney Disease: Therapeutic Efficacy and Nephrotoxic Implications

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ABSTRACT

Broad classes of naturally occurring polyphenolic chemicals, anthraquinones are present in medicinal plants like Rheum, Cassia, and Aloe species. They have a complicated pharmacological profile that includes both toxicological and therapeutic aspects. Growing interest in their potential uses for renal diseases such as diabetes-related nephropathy, renal fibrosis, and ischemia–reperfusion injury has been sparked by their pleiotropic bioactivities, which include anti-inflammatory, antioxidant, antifibrotic, and cytoprotective properties. Anthraquinones can reduce both inflammation and oxidative stress by modifying glomerular and tubular functioning, enhancing redox balance, and controlling important signaling pathways like NF-κB, MAPK, and TGF-β at pharmacologically relevant dosages. However, prolonged or excessive exposure, especially from laxatives containing anthraquinone, has been linked to nephrotoxicity, which is characterized by oxidative damage, mitochondrial dysfunction, and tubular apoptosis. These substances are deemed inappropriate for long-term use by regulatory bodies including the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) because of the possibility of kidney impairment and cancer. Developments in prodrug design, targeted drug delivery, formulation science, and combined administration with nephroprotective adjuncts present viable ways to maximize therapeutic effectiveness while reducing renal toxicity. This review integrates clinical and translational evidence, discusses current gaps and future directions for safer therapeutic exploitation of this double-edged phytochemical class, and provides a thorough summary of the chemical structure, pharmacokinetics, pharmacodynamics, and molecular principles underpinning the dual renal effects of anthraquinones.

INTRODUCTION

About 14.2% of the world's population suffers from kidney illnesses, which include both acute kidney injury (AKI) and chronic kidney disease (CKD). These conditions significantly increase morbidity, mortality, and healthcare expenses (1).

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The present therapeutic picture for renal illnesses is still primarily supportive, with few medications able to stop or reverse renal injury, despite advances in dialysis and transplantation. As a result, research into natural compounds and phytochemicals as possible renal function modulators and nephrotoxicity defenders has grown (2).Anthraquinones, one of the many substances generated from plants, have garnered a lot of pharmaceutical interest due to their diverse biological properties. Anthraquinones are tricyclic aromatic quinones (anthracene-9,10-dione derivatives) that are found in several medicinal plants, including Polygonum multiflorum, Rheum palmatum (rhubarb), Cassia angustifolia (senna), and Aloe vera (3). These substances have historically been employed as hepatotonics and purgatives in a number of medical systems, including Ayurveda and Traditional Chinese Medicine. Anthraquinones have been shown to have a variety of pharmacodynamic effects on several organs, including the liver, cardiovascular system, and kidneys, in addition to their traditional laxative effect, which is mediated by stimulation of intestinal peristalsis and water secretion (4).

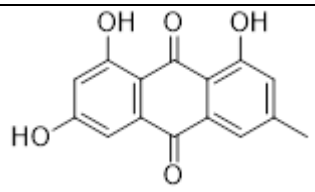
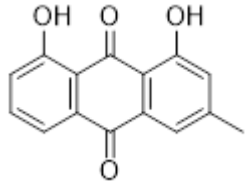
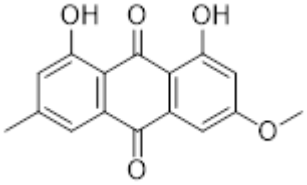
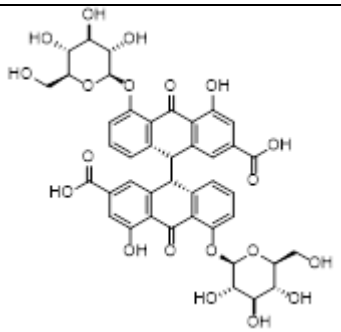
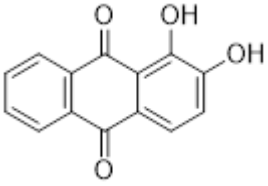
Anthraquinones including rhein, emodin, chrysophanol, and aloe-emodin have shown strong anti-inflammatory, antioxidant, antifibrotic, and nephroprotective effects in the context of renal pharmacology (5). Inhibition of NF-κB and MAPK activation, elevation of Nrf2/HO-1 antioxidant defense, and reduction of TGF-β/Smad signaling involved in renal fibrosis are among the molecular signaling pathways fundamental to kidney pathology that are modulatedto mediate these effects (6). For instance, emodin shields renal tubular cells from cisplatin-induced death by modifying mitochondrial and oxidative processes, whereas rhein attenuates diabetic nephropathy by lowering extracellular matrix buildup and oxidative stress (7).However, exposure to anthraquinone has two distinct pharmacological effects. In experimental models, a number of derivatives show renoprotective benefits; however, long-term or high-dose use, especially from herbal laxatives, has been linked to tubulointerstitial nephritis, pigment nephropathy, and electrolyte imbalances, indicating dose-dependent nephrotoxicity . Anthraquinones are therefore a pharmacological paradox because their potential for renal damage is intimately linked to their therapeutic potential. A major obstacle to clinical translation is still comprehending the delicate balance between helpful modulation and harmful insult.Our knowledge of the renal disposition of anthraquinones has been considerably enhanced by new pharmacokinetic and translational research. The kidney is both a target and a vulnerable organ for these drugs' effects due to their considerable hepatic metabolism, enterohepatic recirculation, and renal excretion (8). Enhancing efficacy while reducing systemic and renal toxicity has been the goal of efforts to create colon-targeted or nano-formulated delivery methods (9). When considered collectively, the data indicate that anthraquinones have a complex role in renal pharmacology, impacting both pathogenic and beneficial processes. By examining molecular processes, disease-specific effects, experimental discoveries, and translational potential, this review seeks to thoroughly investigate their dual role as nephrotoxic chemicals and reno-protective drugs. The ultimate objective is to present an integrative viewpoint that could guide the development of anthraquinone-based medications with improved safety and effectiveness characteristics in the future.

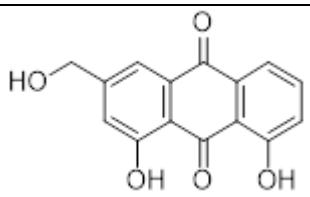
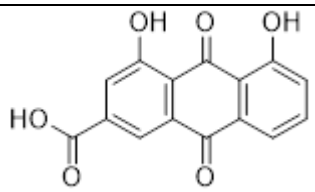
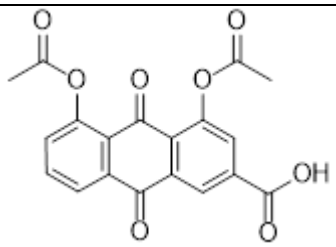
2. Chemistry and sources of anthraquinones

The structural building blocks of anthraquinones, also known as anthracenediones or

dioxoanthracenes, are an anthracene ring with the keto groups at positions 9 and 10 and a variety of functional groups including -OH, -OCH_3, -CH_3, -CH_2OH, -CHO, and –COOH (Özgen, et al., 2025). They are widely distributed in nature—plant families including Polygonaceae (e.g., *Rheum* spp.), Rubiaceae (e.g., *Rubia* spp.), Asphodelaceae (e.g., *Aloe* spp.) and Fabaceae (e.g., *Cassia* spp.) produce free anthraquinones and anthraquinone glycosides in roots, rhizomes or leaf tissues (10). Their biosynthesis through the acetate/malonate (polyketide) pathway, which involves successive condensations of acetyl-CoA/malonyl-CoA units to form a polyketide chain that subsequently goes through cyclization, oxidation, and post-synthetic modifications like methylation, hydroxylation, and glycosylation, is responsible for this group's structural diversity (11).The main naturally occurring anthraquinones, together with their structure, botanical sources and reported pharmacological significance are mentioned in table1.

Table 1: The main naturally occurring anthraquinones

Compound	Structure	Major source	Reported pharmacological/ Renal relevance	References
Emodin		*Rheum palmatum*, *Aloe vera*	Anti-inflammatory, anti-fibrotic, antioxidant; mitigates renal fibrosis via inhibition of the TGF-β signalling pathway.	12
Chrysophanol		*Rheum officinale*	Antioxidant and nephroprotective; reduces oxidative stress and inflammation in diabetic nephropathy models.	13
Physcion		*Cassia tora*	Exhibits anti-inflammatory effects; ameliorates liver fibrosis	14,15
Sennoside A/B		*Cassia angustifolia*	Laxative glycosides; chronic exposure or misuse associated with renal tubular damage and electrolyte imbalance.	16
Alizarin		*Rubia cordifolia*	Displays antioxidant, anti-fibrotic and anti-calcific activities in renal tissue; prevents calcium oxalate deposition.	17

Aloe emodin		Aloe and Rhubarb	Helps suppressing renal fibrosis progression; exerts hepatoprotective, anti-viral and anti-inflammatory activity.	18,19
Rhein		*Rheum paltatum*	Antioxidant and anti-inflammatory activity; reduce kidney damage; decrease kidney inflammation by reducing oxygen free radical levels	6,20,21
Diacerein		*Aloe vera* and Rhubarb	Anti-inflamamtory, help prevent elevated blood glucose levels	22

3. Pharmacokinetics aspects of anthraquinones

Anthraquinones' complex pharmacokinetic behavior is impacted by their degree of glycosylation, structural alterations, and physicochemical characteristics. Their physical and chemical characteristics, particularly their quinone architecture and their ability to dissolve under typical circumstances, determine how well they are absorbed. The intestines are where anthraquinones are primarily absorbed , and because of their greater lipophilicity, free aglycone forms are absorbed more quickly than glycosylated forms (9). The mean time to achieve maximum plasma concentration for a rhubarb extract including aloe-emodin, rhein, emodin, chrysophanol, and physcion was reported to be between 0.42 to 0.75 hours after an oral dose in rats, showing fast absorption (23). Prior to absorption, intestinal microbiota (β-glucosidases/reductases) hydrolyzes a lot of nthraquinone glycosides (like sennosides and aloin) to dianthrone/anthrone aglycones (like rheinanthrone and emodin). Sennoside conversion in the large intestine is quick and efficiently finished in a matter of hours (24). After being absorbed, anthraquinones go through a lot of phase II metabolism, mostly glucuronidation and sulfation, which is why glucuronide/sulfate conjugates, not parent aglycones, are frequently the forms that circulate in plasma (25). Studies on tissue distribution reveal that anthraquinones and/or their conjugates consistently accumulate in the liver, kidney, and gut, with variations at the organ level (for instance, the liver has a comparatively high amount of free emodin, but the kidney and lung have more conjugates)(26,27). Comprehensive metabolic studies revealed that emodin has a total bioavailability of approximately 3.2%. Approximately 56% of the supplied dose goes unabsorbed and is mostly eliminated in the feces as the unaltered chemical. The absorbed percentage is rapidly metabolized, primarily by hydroxylation and glucuronidation. The kidney is primarily responsible for the distribution of both the parent substance and its metabolites in the body (28). Enterohepatic circulation of glucuronidated and sulfated metabolites is a common pharmacokinetic feature of

anthraquinones, often leading to secondary plasma concentration peaks or prolonged apparent terminal elimination, thus extending tissue exposure and complicating pharmacokinetic-pharmacodynamic (PK-PD) correlations (29). The pharmacokinetics of anthraquinones are significantly altered by pathophysiological conditions and co-administered herbal ingredients (e.g., illness models exhibit higher Cmax/AUC and longer t½ for various anthraquinones) (9).

4. Pharmacodynamic aspects of anthraquinones

The pharmacodynamic effects of anthraquinones, a broad class of bioactive chemicals, are varied and include anti-inflammatory, anti-cancer, antibacterial, antioxidant, and metabolic regulating activities (30). These compounds have been shown to exert potent anti-inflammatory effects through inhibition of the NF-κB signalling pathway and MAPK cascades, thereby suppressing the release of pro-inflammatory cytokines (TNF-α, IL-6) and reducing COX-2 and iNOS expression (12).Pharmacodynamically, anthraquinones show a distinct dose-response relationship: low to moderate doses enhance antioxidant defenses (SOD, CAT, and GSH-Px) and inhibit NF-κB and MAPK signaling, resulting in antioxidant, anti-inflammatory, and cytoprotective effects; high or chronic doses, on the other hand, can cause pro-oxidant and cytotoxic effects because of mitochondrial dysfunction and ROS overproduction (31,32).

5. Role of anthraquinones in renal pharmacology

By altering oxidative, inflammatory, and fibrotic pathways, as well as renal transporters and electrolyte management, anthraquinones have a variety of impacts on renal physiology. Depending on the dosage and length of exposure, these processes work synergistically to produce both renoprotective and nephrotoxic effects.

5.1 Antioxidant and anti-ferroptotic effects

One of the main causes of kidney damage is oxidative stress. Strong antioxidant action is demonstrated by anthraquinones such emodin, aloe-emodin, and rhein, which scavenge reactive oxygen species (ROS) and restore redox balance via activating the Nrf2/HO-1 pathway (33,34). This lowers lipid peroxidation indicators like malondialdehyde (MDA) and increases antioxidant enzymes including glutathione peroxidase (GPx), catalase (CAT), and superoxide dismutase (SOD). Emodin stabilizes mitochondrial activity and activates Nrf2-mediated antioxidant signaling to significantly reduce oxidative damage and ferroptosis in diabetic and cisplatin-induced nephropathy models (35).

5.2 Anti-inflammatory effects (NF-κB, NLRP3, MAPK Pathways)

A primary pathogenic factor in chronic kidney disease (CKD), inflammation is intimately associated with the development of renal fibrosis. Leukocyte recruitment, cytokine release, and the consequent activation of profibrotic pathways are all facilitated by persistent inflammatory signaling (34). In models of renal damage, anthraquinones like emodin and rhein have strong anti-inflammatory effects by modifying important intracellular signaling cascades linked to immunological responses.

Emodin inhibits the activation of the AIM2 (Absent in melanoma 2)inflammasome, a cytosolic sensor linked to chronic inflammatory damage in renal fibrosis, according to one mechanistic research. Emodin decreased serum inflammatory cytokines (TNF-α and IL-1β) in

mice with unilateral ureteral obstruction (UUO), inhibited important AIM2 inflammasome signaling components like ASC(Apoptosis-associated speck-like protein containing a CARD) and cleaved caspase-1, and attenuated the deposition of extracellular matrix proteins (such as collagen I and α-smooth muscle actin) (36).

Furthermore, a thorough analysis of Rheum officinale anthraquinones reveals that they modulate pro-inflammatory pathways, such as NF-κB signaling inhibition and IκB/NF-κB uptake regulation, which collectively suppress transcription of pro-inflammatory cytokines and chemokines in models of chronic kidney disease and acute kidney injury (34).

Anthraquinones, such as rhein and aloe-emodin, have been demonstrated in other organ systems to inhibit NLRP3 inflammasome assembly and downstream IL-1β activation, despite the paucity of direct evidence on the NLRP3(NOD-like receptor family, pyrin domain-containing protein 3)inflammasome in renal models. This suggests a plausible shared mechanism that merits additional investigation in renal fibrosis research (37).

All of these findings point to anthraquinones' anti-inflammatory function in chronic kidney disease (CKD) through the inhibition of innate immune signaling pathways, the decrease of inflammatory cytokines, and the attenuation of inflammasome activation. These mechanisms are intimately related to the prevention of the progression of fibrosis as well as the maintenance of renal structure and function.

5.3 Anti-fibrotic activity (TGF-β/Smad Signaling)

The primary pathogenic feature of chronic kidney disease (CKD) is renal fibrosis, which is primarily caused by pro-fibrotic signaling cascades like the transforming growth factor-β1 (TGF-β1)/Smad pathway being continuously activated. Tubulointerstitial fibrosis and the loss of functional nephrons are caused by the activation of TGF-β1, which phosphorylates receptor-regulated Smads (Smad2 and Smad3) and causes their nuclear translocation. This results in the transcription of extracellular matrix (ECM) genes, such as collagen I, fibronectin, and α-smooth muscle actin (α-SMA).

In CKD experimental models, anthraquinone derivatives block these pathways to produce anti-fibrotic effects. Rhubarb extracts high in anthraquinones dramatically inhibited the TGF-β/Smad signaling axis in a rat model of CKD caused by adenine. TGF-β1, TGF-β receptors I and II, Smad2, phosphorylated Smad2/3, Smad3, and Smad4 were all reduced in expression as a result of treatment, however the inhibitory Smad7 was increased. The potential of anthraquinone-based extracts to rebalance pro-fibrotic signaling in vivo was highlighted by this modulation, which resulted in decreased ECM deposition, better histopathology, and partial restoration of metabolic abnormalities linked to CKD-related fibrosis (38).

Similarly, in TGF-β1-induced cellular systems and unilateral ureteral obstruction (UUO) models, emodin, a well-known anthraquinone, has been demonstrated to reduce renal fibrosis. Treatment with emodin decreased activation of TGF-β1-induced fibrotic phenotypes, improved kidney histopathological characteristics, and decreased fibrosis biomarkers. According to Feng et al. (2024), emodin's anti-fibrotic effects are mechanistically related to the regulation of mitochondrial homeostasis, which is mediated by peroxisome proliferator-activated receptor-gamma coactivator-1 alpha (PGC-1α). This

suggests that attenuated fibrogenesis is a result of modulating cellular energy and metabolic stress.

In addition to directly inhibiting TGF-β/Smad, anthraquinones, such as rhein, also have anti-fibrotic effects by modifying metabolic and signaling pathways that interact with fibrogenic processes. Rhein reduced epithelial–mesenchymal transition (EMT), a major factor in myofibroblast formation, in experimental models of renal fibrosis by restoring fatty acid oxidation via the Sirtuin1 (Sirt1)/STAT3/Twist1 pathway (39)

All of these investigations show that anthraquinones reduce renal fibrogenesis by suppressing EMT pathways, regulating cellular metabolism, and multi-targetedly inhibiting TGF-β1/Smad signaling. The consistent inhibition of pro-fibrotic mediators across models supports therapeutic exploration of anthraquinones as modulators of renal fibrosis in chronic kidney disease (CKD), even though a large portion of this evidence is preclinical.

5.4 Modulation of Renal Transporters and Pharmacokinetic Interactions

The dysregulation of organic anion transporters (OAT1 and OAT3), which facilitate the excretion of protein-bound uremic toxins such indoxyl sulfate and p-cresyl sulfate, is one of the main ways that tubular dysfunction contributes to the development of chronic kidney disease (CKD). In proximal tubular epithelial cells, downregulation of these transporters worsens oxidative stress, inflammatory signaling, and toxin accumulation. Anthraquinone-rich rhubarb extract markedly suppressed TGF-β1/Smad signaling and restored OAT1 and OAT3 expression in the adenine-induced CKD rat model. Additionally, metabolomic study showed enhanced removal of endogenous compounds linked to uremic damage. These results imply that anthraquinones may maintain tubular excretory function as a result of structural and metabolic recovery as opposed to direct transporter agonism (38).

Rhein, an anthraquinone obtained from Rheum palmatum, showed mitigation of the epithelial–mesenchymal transition (EMT) by restoring fatty acid oxidation via the Sirt1/STAT3/Twist1 pathway, in addition to extract-level effects. Inhibiting EMT indirectly stabilizes tubular transport networks and solute handling because it alters tubular polarity and transporter expression (39).

5.5 Diuretic and electrolyte-modulating effects

Although plants that contain anthraquinone, including aloe vera and senna (Cassia angustifolia), have long been utilized for their laxative qualities, there is evidence that they also have impacts on renal electrolyte management. Anthraquinones may affect water reabsorption and tubular sodium transport by modifying aquaporin expression (40). Mild diuretic effects may be exacerbated by increased excretion of water and salt. However, because of increased potassium loss, extended exposure has been linked to electrolyte abnormalities, including hypokalemia. Such imbalances may worsen arrhythmogenic risk and affect renal hemodynamics in patients with chronic kidney disease (CKD), underscoring the significance of controlled dosage (41).

5.6 Additional Molecular Pathways (AMPK, PI3K/Akt, NOX4)

Anthraquinones alter cellular energy metabolism and survival pathways, according to new research. In renal tubular cells, AMP-activated protein kinase (AMPK) activation promotes mitochondrial biogenesis and lowers metabolic stress. Emodin has been shown to enhance mitochondrial function and reduce oxidative

damage via activating AMPK (42). In renal injury models, anthraquinones also contribute to cytoprotection through their influence on the PI3K/Akt pathway, which is essential for cell survival and anti-apoptotic signaling (43). Moreover, mitochondrial ROS generation and fibrogenic signaling are decreased by downregulating NADPH oxidase 4 (NOX4), a significant generator of renal reactive oxygen species (44). Anthraquinones demonstrate multi-target pharmacological activity in renal systems by means of the coordinated modulation of the AMPK, PI3K/Akt, NOX4, NF-κB, and TGF-β pathways. Nevertheless, translational limitations, dose-dependent toxicity, and insufficient long-term clinical trials remain critical barriers to therapeutic application.

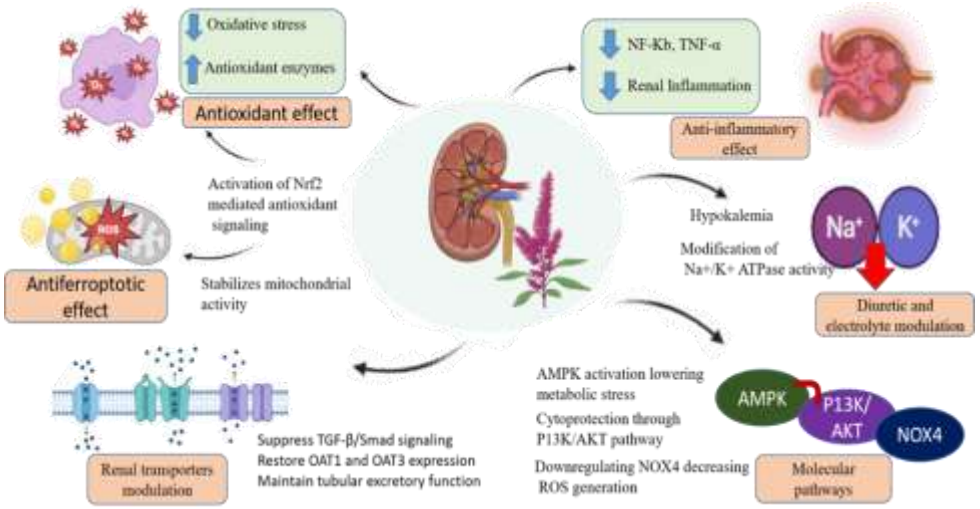


Fig.1: Effects of anthraquinones in renal pharmacology

6. Anthraquinones in renal disorders

Anthraquinones are now recognized as significant phytochemicals that may be used to treat a range of renal conditions. Their main impact is ascribed to their capacity to reduce oxidative stress, inflammation, and fibrosis—three important mechanisms that underlie the development of kidney injury. Rhein, emodin, aloe-emodin, and chrysophanol are the anthraquinones that have been studied the most for their renoprotective qualities in a variety of disease settings.

6.1 Diabetic Nephropathy (DN)

Glomerular hypertrophy, thickening of the basement membrane, and interstitial fibrosis brought on by persistent hyperglycemia and inflammation are the hallmarks of diabetic nephropathy. Rheum palmatum is the source of Rhein, an anthraquinone that has been demonstrated to dramatically enhance renal function in diabetic animals (45). It decreases extracellular matrix deposition by inhibiting the production of fibronectin, connective tissue growth factor (CTGF), and TGF-β1.Rhein also reduces macrophage infiltration in renal tissue by blocking NF-κB activation (46,47). Proteinuria and serum creatinine levels in individuals with early DN were shown to improve in clinical settings when rhein-containing preparations were used (50).Similarly, emodin prevents DN by enhancing glucose metabolism, inhibiting mesangial growth, and activating AMPK and mTOR (48).

6.2 Acute Kidney Injury (AKI)

Abrupt loss of renal function brought on by ischemia, toxins, or inflammation is known as

acute kidney injury. Renal ischemia/reperfusion injury has been shown to be lessened by anthraquinones such as emodin and aloe-emodin. They accomplish this by inhibiting tubular apoptosis, lowering lipid peroxidation, and activating the Nrf2/HO-1 pathway (49,5).Additionally, Rhein protects against cisplatin-induced nephrotoxicity by downregulating the production of TNF-α and IL-1β and restoring antioxidant enzyme activity (SOD, GSH-Px) (50). These results demonstrate anthraquinones' potential as adjuncts to lessen chemotherapy's nephrotoxic adverse effects.

6.3 Chronic Kidney Disease (CKD) and renal fibrosis

Mostly found in Rheum species (rhubarb), anthraquinones including rhein, emodin, aloe-emodin, and chrysophanol have drawn interest from researchers due to their potential to alter key pathways involved in the development of renal fibrosis and chronic kidney disease (CKD). One of the main factors influencing the progression of chronic kidney disease (CKD) to end-stage renal disease is renal fibrosis, which is defined by excessive extracellular matrix (ECM) deposition triggered by profibrotic signaling. By improving mitochondrial homeostasis through the upregulation of peroxisome proliferator-activated receptor-gamma coactivator-1 alpha (PGC-1α), emodin has demonstrated significant antifibrotic effects in preclinical models. This is linked to decreased expression of fibrosis markers and attenuated histopathological renal damage in unilateral ureteral obstruction (UUO) models, indicating that mitochondrial stabilization may be a significant antifibrotic mechanism (36,51,52,53).Rhein has been shown to decrease the advancement of fibrosis by blocking TGF-β1/Smad3 signaling, which is a key factor in the creation of ECM proteins and the activation of myofibroblasts (6). Chrysophanol and other anthraquinones inhibit NF-κB-mediated inflammatory pathways, which are intimately associated with profibrotic signaling in chronic kidney disease (CKD) (54). Numerous anthraquinones have been found to interact with CKD-related targets through network pharmacology and experimental validation. They reduce renal fibrosis and inflammation by inhibiting the activation of the NF-κB pathway and downregulating pro-inflammatory cytokines like IL-6, IL-1β, and TNF-α (51).Although there is still a lack of direct histological data in humans, clinical randomized controlled trials and observational studies of rhubarb-containing preparations in CKD patients have shown improvements in renal biochemical markers and decreases in proteinuria, outcomes that correlate with slowed fibrotic progression. All of these results point to the possibility that anthraquinones may target several signaling pathways (such as TGF-β/Smad, NF-κB, and mitochondrial regulation) to provide renoprotective and antifibrotic effects, which would warrant further research into them as CKD management adjuncts(6,55).

6.4 Drug-induced nephrotoxicity

A number of nephrotoxic substances cause oxidative and inflammatory kidney damage, including cyclosporine, gentamicin, and cisplatin. By blocking MAPK signaling and preserving mitochondrial integrity, emodin lessens the nephrotoxicity caused by gentamicin (56). Anthraquinones also inhibits endoplasmic reticulum stress and caspase-12 activation to prevent cyclosporine-induced kidney injury (57). The use of anthraquinones as nephroprotective adjuvants is supported by these findings.

6.5 Renal carcinoma and other disorders

Recent research suggests that anthraquinones may have anticancer potential against renal cell carcinoma (RCC), albeit limited. Emodin suppresses PI3K/Akt signaling and triggers death in RCC cells through ROS-mediated mitochondrial pathways (58). Furthermore, the antioxidant and anti-inflammatory effects of anthraquinones have shown promise in glomerulonephritis and renal cystic diseases, though more clinical data are required (59).

7. Anthraquinone induced nephrotoxicity

Anthraquinones have potential nephrotoxic effects despite their promise therapeutic uses, especially when used in large quantities or for an extended length of time. Although their redox-active quinone structure has numerous therapeutic advantages, it can also produce reactive oxygen species (ROS), which can result in renal dysfunction, tubular cell damage, and oxidative stress. The necessity of dose standardization and safety assessment in both pharmaceutical and herbal formulations is highlighted by this paradoxical result.

7.1 Mechanisms underlying anthraquinone-induced nephrotoxicity

The main mechanisms by which anthraquinones cause nephrotoxicity are oxidative stress, mitochondrial damage, and renal tubular epithelial cell death. ROS can be produced by redox cycling when anthraquinone metabolites, such as rhein anthrone and aloe-emodin anthrone, accumulate excessively (60). Tubular necrosis results from lipid peroxidation, intracellular glutathione (GSH) depletion, and caspase-3 activation (61).Additionally, through intrinsic apoptotic pathways, anthraquinones can promote cell death by reducing ATP and impairing mitochondrial oxidative phosphorylation. By fragmenting DNA and depolarizing the mitochondrial membrane, some derivatives, like danthron and chrysazin, directly cause cytotoxicity in proximal tubular cells (62).Modification of renal transporters, such as organic anion transporter 1 (OAT1) and OAT3, which are in charge of drug and metabolite clearance, is another contributory factor. These transporters are competitively inhibited by high anthraquinone dosages, which may cause hazardous intermediates to accumulate intracellularly (63).

7.2 Histopathological and experimental evidence

Research on animals has shown that long-term use of rhubarb extracts or laxatives containing anthraquinone causes tubulointerstitial fibrosis and pigment nephropathy. Histological observations include the development of brown pigment granules in renal tissue, interstitial inflammation, and tubular epithelial degradation (64). Long-term administration to rhein (≥100 mg/kg/day) in mice caused mitochondrial enlargement, tubular dilatation, and increased serum creatinine (6). Similarly, emodin confirmed oxidative damage by causing localized tubular necrosis and elevated renal malondialdehyde (MDA) levels at high dosages (65).

7.3 Clinical Reports and Human Observations

Long-term use of herbal laxatives based on anthraquinone, such rhubarb, cascara, and senna, has been associated in a number of clinical case reports with melanosis coli and chronic kidney damage, which can occasionally lead to renal papillary necrosis (37). In a few cases, people who consumed herbal mixes containing emodin and rhein derivatives also experienced acute interstitial nephritis (37). These symptoms emphasize the thin safety margin between therapeutic and dangerous doses, even though they are usually reversible upon cessation. A case report published in the

Hong Kong medical journal gives one of the most convincing clinical observations in humans that connects anthraquinone derivatives to renal disease. After using a patented herbal slimming pill that contained anthraquinone derivatives derived from rhubarb for an axtended period of time , a 23 year old lady experienced acute renal failure. Although renal function improved after stopping the medication , minor interstitial fibrosis and tubular atrophy remained histologically four months later, according to renal biopsy that revealed hypocellular interstitial fibrosis (66).

7.4 Structure–Toxicity Relationship

The pattern of chemical substitution in anthraquinones affects their potential for nephrotoxicity. Because of their increased redox cycling potential, hydroxylated anthraquinones (such as emodin and aloe-emodin) tend to produce more ROS, while their methylated or glycosylated equivalents are less hazardous (67). Conjugation by sulfation or glucuronidation increases renal excretion and decreases cytotoxicity, indicating that structural changes may provide safer compounds for medicinal application.

7.5 Strategies to Mitigate Toxicity

Researchers have suggested the following to reduce the risk of nephrotoxicity,regulated dosage and brief anthraquinone administration,co-administration of antioxidants to counteract ROS, such as quercetin and N-acetylcysteine,creation of focused medication administration methods that improve kidney selectivity,CYP450 and OAT interaction screening prior to clinical use (30).

8. Strategies to enhance therapeutic efficacy and minimize toxicity:

A multifaceted approach is advised to maximize the beneficial effects of anthraquinones in renal illness while reducing nephrotoxicity. First, pro-drug design or structural change can increase solubility, decrease unwanted renal tubular absorption, and promote localized activation of the active ingredient (68). Second, sustained release, decreased peak plasma concentrations, and less off-target renal exposure are made possible by targeted drug delivery methods and nanoparticle formulations (38). Third, the therapeutic window is further expanded and tubular damage caused by oxidative stress and apoptosis is decreased by co-administration of nephroprotective drugs, such as antioxidant or anti-inflammatory adjuncts, and optimization of dosage regimens (avoiding high Cmax, lowering frequency or dose) (69). Fourth, early monitoring employing sensitive renal biomarkers (e.g., KIM-1, NGAL) and modification of pertinent metabolic pathways (e.g., favoring glucuronidation over oxidative activation) aid in the detection of renal injury prior to overt toxicity (70). Individualized treatment and enhanced safety are made possible by patient selection and continuous renal function monitoring, particularly in individuals with pre-existing CKD or concurrent nephrotoxins. Last but not least, incorporating "safety-by-design" principles—like PK/PD modeling, mechanism-based toxicology (e.g., ferroptosis via Nrf2/GPX4 pathways, mitochondrial malfunction) and early in-vitro renal tubular cell screening—supports translation into the clinic with a lower risk of nephrotoxicity (71).

9. Clinical and Translational Evidence

Although there is still a lack of human clinical evidence, emerging translational research supports the renoprotective potential of important anthraquinones including rhein and emodin. While emodin reduces high-glucose-induced podocyte damage and renal fibrosis by activating AMPK/mTOR-mediated autophagy and Nrf2-

driven antioxidant responses, rhein has been demonstrated to improve urinary albumin excretion and renal histopathology in diabetic nephropathy (DN) models by blocking TGF-β1/Smad signaling and oxidative stress (50). These drugs have poor oral bioavailability but high renal tissue accumulation, according to pharmacokinetic modeling, indicating both a therapeutic possibility and the necessity for rigorous safety investigation (72).As a result, kidney-targeted rhein liponanoparticles and other nanoparticle-based delivery systems have been created to improve renal selectivity and lower systemic exposure, and they have shown promise in animal DN models (42). These translational developments highlight a feasible route toward clinical testing of anthraquinones for renal disease, even though regulatory agencies advise against long-term use of anthraquinone-based laxatives due to possible nephrotoxicity, as long as standardization, formulation optimization, and early biomarker-guided safety monitoring are put into place.

CONCLUSION

A pharmacologically diverse class, anthraquinones have been shown to have renoprotective effects in a variety of experimental animals. Compounds like rhein and emodin are intriguing lead scaffolds for kidney-directed therapies because of their ability to inhibit fibrotic development, control inflammatory cascades, and reduce oxidative stress. Translational developments, such as better formulations and focused delivery methods, present encouraging approaches to boost effectiveness while reducing systemic toxicity.However, safety concerns limit the clinical translation of anthraquinones: in animal studies and case reports from human herbal product use, prolonged or high-dose exposure has been linked to tubular injury and interstitial fibrosis, highlighting the necessity of thorough toxicokinetic profiling and carefully planned clinical trials. In order to identify early benefits or harm, future research should focus on randomized clinical trials that include sensitive renal biomarkers (e.g., NGAL, KIM-1, and cystatin C), standardized botanical preparations or synthetic analogs with improved therapeutic indices, and structure–activity relationship (SAR) studies. Anthraquinones may replace conventional treatments as logically formulated medicines in renal pharmacotherapy with proper optimization and safety assessment.

CONFLICT OF INTEREST

No

FUNDING

No

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