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A Review on the Nephroprotective Role of Flavonoid-Rich Substances in Doxorubicin-Treated Animal Models

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Abstract:

Cancer continues to pose a significant global health challenge, affecting nearly one in five individuals throughout their lifetime. While chemotherapeutic agents like doxorubicin play a crucial role in cancer treatment, their use is frequently accompanied by serious side effects, particularly nephrotoxicity. This review critically examines the renoprotective effects of flavonoids in counteracting doxorubicin-induced kidney damage, with a focus on evidence from preclinical animal models. Doxorubicin mediates its cytotoxic effects by intercalating into DNA and inducing the formation of reactive oxygen species (ROS), which lead to oxidative stress, apoptosis, and subsequent renal injury. A comprehensive literature search was conducted using databases including Google Scholar, Scopus, pubmed, Springer, Wiley Online Library, and sciencedirect, targeting articles published between 2014 and 2024. Keywords used included "flavonoids," "doxorubicin," "nephrotoxicity," "Renoprotective," and "animal model." Flavonoids, a broad class of plant-derived polyphenols, are well recognized for their antioxidant, anti-inflammatory, and anticancer activities. Certain flavonoids, similar to quercetin, rutin, kaempferol, morin, luteolin, apigenin, hesperidin, naringenin, diosmin, and anthocyanins, have shown significant effectiveness in reducing kidney damage caused by doxorubicin. This review highlights the promising role of flavonoids as potential adjuvants in reducing chemotherapy-associated renal side effects and enhancing the safety profile of anticancer regimens.

Key Words:

Cancer, Flavonoids, Doxorubicin, Nephrotoxicity, Renoprotection.

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1. Introduction

Cancer has emerged as one of the most formidable health challenges worldwide, with current estimates indicating that one in every five individuals will be diagnosed with the disease during their lifetime. According to global projections for the year 2022, approximately 20 million new cancer cases were expected, with nearly 10 million cancer-related deaths reported [1]. Chemotherapeutic agent are chemical drugs that stop cancer cells from growing and proliferating unrestrained by killing and suppressing them [2]. One powerful chemotherapeutic drug that effectively targets and cures a variety of cancer forms is doxorubicin. As an anthracycline medication, doxorubicin is generated from the Streptomyces peucetius bacteria and is closely related to antibiotic medications [3, 4].

Doxorubicin is used to treat a variety of cancer patient tumor types, providing therapeutic benefits via a multifaceted method including several cell death pathways, such as apoptosis, pyroptosis, ferroptosis, and necroptosis [5-7]. Also, doxorubicin affects cancer cells in a variety of ways, including by intercalating into the DNA double helix and producing free radicals that disrupt topoisomerase II-mediated DNA repair, causing damage to proteins, DNA molecules, and cell membranes [8]. ROS are produced in the later stage when doxorubicin undergoes oxidation to produce semiquinone, an unstable metabolite that is subsequently transformed back into doxorubicin [9]. Despite its strong anticancer properties, doxorubicin can cause side effects and other problems, including hepatotoxicity, cardiotoxicity, and nephrotoxicity, when used as a chemotherapeutic drug over an extended period of time [10-12]. Nephrotoxic effects of doxorubicin can be detected by glomerular pathology and the onset of nephrotic syndrome-related clinical symptoms [13]. In the human body, the kidney is a vital organ that absorbs a large amount of blood (25% of cardiac output) and removes medications and metabolic products from the circulation as urine [14]. Urine is formed in the kidneys by three processes: tubular secretion, tubular reabsorption, and glomerular filtration. Kidney injury through doxorubicin drug causes damage and renal failure can result from that cause these nephron cell damage [15].

Medicinal plants are frequently used by specific cultures in their traditional medical practices [16]. Flavonoids, a variety of polyphenolic chemicals that are prevalent in the flowers, leaves, stems, and fruits of plants, are among the numerous secondary metabolite substances found in natural plants [17]. Additionally, flavonoids provide a number of pharmacological advantages, such as anti-inflammatory, anti-cancer, antitumor, neuroprotective, antioxidant, antiviral, antibacterial, and anti-angiogenic properties [18-20]. Flavonoids are divided into a number of groups, such as anthocyanidins, flavonols, flavones, flavanones, and isoflavonoids [21]. These substances efficiently increase the production of defensive enzymes such nuclear factor erythroid 2-Related Factor 2 (NRF2), glutathione (GSH), catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPx) [22], [23] Moreover, flavonoids reduce the levels of pro-inflammatory proteins like Tumor Necrosis Factor-α (TNF-α), Nuclear Factor-κB (NF-κB), Interleukin-1β (IL-1β), and Interleukin-6 (IL-6) while suppressing the expression of pro-apoptotic proteins like Cytochrome C (Cyt C), B-Cell Lymphoma 2(BCL-2)-associated X protein (BAX), and caspase-3, caspase-7, and caspase-9 [4, 24] Reviewing the renoprotective efficacy of flavonoids against doxorubicin-induced kidney injury in experimental animal models is the goal of this work. In order to get relevant data on the effects of flavonoid-rich compounds as a renoprotective medication in animal models produced by doxorubicin, this literature review was conducted. Research on the terms "flavonoids, doxorubicin, renoprotective, nephrotoxicity, and animal model" was gathered from famous databases across the world, including Google Scholar, Scopus, PubMed, Springer, Wiley Online Library, and ScienceDirect. Publications from 2014 to 2024, which span the last ten years, are the main focus. To make sure no important information on flavonoids is missed, a few papers from before to 2013 have been added. To make sure this story is comprehensive, we also took into account the relevant references given in these publications.

Mechanism of doxorubicin action

One common chemotherapeutic agent is doxorubicin. The Streptomyces paucities bacterium is the source of doxorubicin, an anthracycline medication that is closely related to antibacterial medications [25]. That being said, it is still unclear exactly how doxorubicin works [8]. According

to some sources, doxorubicin functions as a cancer chemotherapeutic medication by a complicated process that includes ROS generation, DNA intracellularity, and Topoisomerase II inhibition [26]. Doxorubicin in the causes DNA damage and long time uses they causes oxidative stress and kidney damage [27]. Inhibiting vital macromolecular production processes, doxorubicin reaches the nucleus of cancer cells passively across the cell membrane by creating doxorubicin complexes in the form of 20s proteasome subunits and penetrating between DNA bases [28]. Because of its aglyconic and daunosamine group structure, doxorubicin interacts with ribo nucleic acid (RNA) and DNA to stretch and break DNA double chains, which prevents cancer cell DNA replication and transcription. Furthermore, the action of doxorubicin, which paralyzes topoisomerase II, inhibits normal DNA replication, preventing the formation of accurate DNA copies and halting the growth of cancer cells. This is because the enzyme topoisomerase II, which is involved in opening and closing DNA strands during DNA replication and repair, is inhibited when doxorubicin intercalates with DNA [29]. The suppression of the DNA replication-related topoisomerase II enzyme by doxorubicin may be a factor in the generation of ROS [30].

Doxorubicin can increase the production of ROS through several mechanisms in cancer cells and they cause oxidative stress. The conversion of doxorubicin to semiquinone doxorubicin by mitochondrial Nicotinamide Adenine Dinucleotide Phosphate (NADPH) oxidase, which produces Superoxide Anion (O_2-) as a byproduct, is one of the primary processes. Furthermore, doxorubicin interacts with the enzyme Nitric Oxide Synthase (NOS), which, in the presence of molecular oxygen (O_2), converts L-arginine to Nitric Oxide (NO) using NADPH as a reductant. Low levels of L-arginine or BH4 can cause NOS to uncouple, generating superoxide. Doxorubicin-generated ROS damage cancer cells' DNA, potentially leading to apoptosis. Additionally, doxorubicin damages the mitochondrial membrane by interacting with cardiolipin, a lipid in the inner mitochondrial membrane. This leads to an increase in ROS generation and damage to the mitochondrial structure, which eventually causes cancer cells to undergo apoptosis [31]. Doxorubicin boosts pro-apoptotic protein expression, decreases anti-apoptotic protein expression, releases Cyt C, and activates caspase-3, leading to excessive ROS production in cancer cells, causing oxidative stress, DNA damage, and cell death [32, 33].

2. Mechanisms of ROS generation in doxorubicin-induced kidney injury

Doxorubicin treatment has been demonstrated to cause ROS production inside the kidney's cytosol and mitochondria [35, 36]. Additionally, the plasma membrane contains the enzyme NADPH Oxidase (NOXs). It could increase ROS production [37]. The breakdown of doxorubicin results in doxorubicin-semiquinone, which quickly oxidizes to create O_2-radicals by transforming molecular [34]. However, NO significantly increases molecular O2 reactivity, which leads to the production of peroxynitrite [38]. Exogenous or internal antioxidants aid in the elimination of ROS by generating hydrogen peroxide (H2O2), which is then transformed into hydroxyl radicals (OH) by the Fenton reaction when iron is present [39, 40]. On the other hand, when doxorubicin is administered in large quantities, the production of ROS increases significantly. Significant increases in ROS generation are brought on by doxorubicin, which clearly causes oxidative damage [41]. The breakdown of lipids in cell membranes, a reduction in ATP levels, the production of peroxynitrite, an increase in ryanodine receptor susceptibility, and eventually mitochondrial dysfunction can all be caused by oxidative stress [6,42]. As a result, excessive calcium (Ca) is released into the cytosol, damaging the mitochondria as well as the cytosol. In the kidneys,

doxorubicin-induced ROS-induced oxidative stress causes inflammatory reactions and apoptosis, triggering pathways like Mitogen-Activated Protein Kinase (MAPK) and NF-κB. These pathways can be identified by biomarkers like IL-6, IL-1β, TNF-α, Kidney Injury Molecule-1 (KIM-1), Neutrophil Gelatinase-Associated Lipocalin (NGAL), and Cystatin C (Cys C), which ultimately results in nephrotoxicity represented in Figure 1 [34].

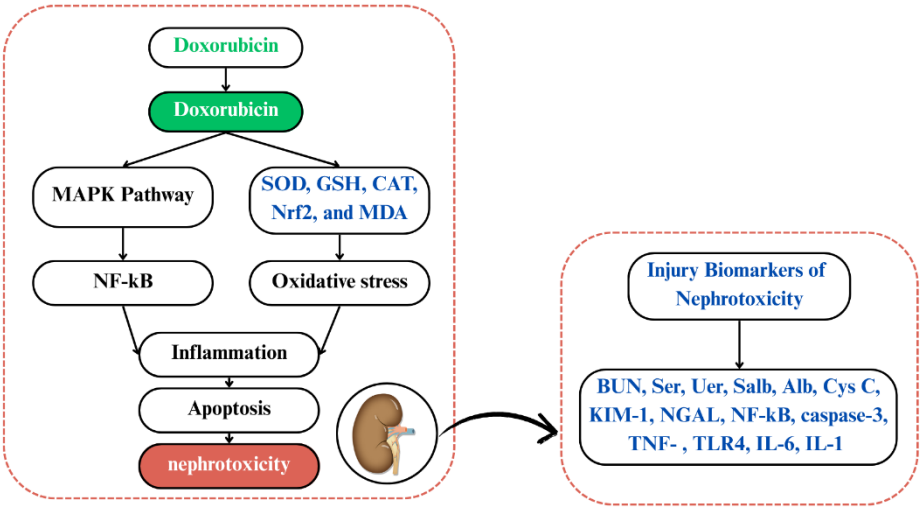

Figure 1: Mechanism of Doxorubicin-Induced Renal Toxicity Through ROS-Driven Oxidative Stress

Injury biomarkers of nephrotoxicity

The main cause of kidney damage following doxorubicin therapy is oxidative stress brought on by ROS. Increased levels of blood urea nitrogen (BUN), serum creatinine (Scr), serum albumin (Salb), and the existence of pathological renal cell death are assessed in the first diagnostic test for chronic kidney damage [43, 44]. Because BUN and SCR tests are susceptible to a number of renal and non-renal variables that are unrelated to kidney function, they are not reliable indicators of kidney function. Additionally, signs of acute renal damage, including proteinuria, can be used to detect kidney nephrotoxicity such as Cys C [45,46]. Lower levels of antioxidant gene biomarker tests, including CAT, SOD, GSH, and NRF2, along with higher levels of malondialdehyde (MDA), can provide strong evidence that oxidative stress is the cause of nephrotoxicity [47-50]. Renal tubular cells produce more transmembrane glycoprotein biomarker KIM-1 when the proximal tubule is damaged [51-53]. An increased NGAL is a trustworthy indicator of kidney damage brought on by exposure to pollutants [54]. Increased amounts of inflammatory factors, such as caspase-3 and NF-κβ [55]. Toll-Like Receptor 4 (TLR4) [56], TNF-α [57], MAPK [58], IL-6, and IL-1β, can lead to inflammation in kidney tissue [59,60]

Kidney tissue disorders due to doxorubicin

Doxorubicin administration may cause a buildup of unpaired electrons in renal tissue proteins, which can be harmful. The kidney tubules and glomeruli may undergo structural and functional alterations as a result, and nephrotic syndrome-related clinical symptoms may appear. Nephrotic syndrome can arise as a result of doxorubicin induction because it disrupts normal mitochondrial function, lowers complex I and complex IV activity, prevents nephron formation, and starts

glomerulosclerosis [61,63]. Due to its main structural elements, renal tubule cells' main function is to act as the kidney's filtration and absorption mechanism. Nephron death can be accelerated by kidney tubular damage or apoptosis, which exacerbates fibrous inflammation [64]. When doxorubicin is administered, some alterations in kidney tissue structure occur. These modifications include the development of vacuoles in the glomeruli bundles' endothelial cells, blood vessel congestion and enlargement in the cortical stroma, a rise in fibroblastic cell proliferation, and localized inflammation between the tubules and cortical glomeruli. Moreover, there may be scarring and localized bleeding in the spaces between the tubules [45,65].

Flavonoids

Flavonoids, phenolic compounds, and bioactive secondary metabolites are produced by a number of plants and may be found in the roots, leaves, seeds, and stems of plants [66]. The molecular structure of flavonoid molecules consists of 15 carbon atoms (C6-C3-C6) arranged in two benzene rings (A and B) connected by a three-carbon bridge [67]. Flavonoid molecules are classified based on the molecule's chemical structure, saturation level, and degree of carbon ring oxidation [68,69]. Flavonoid molecules are categorized into various subclasses like flavonols, flavones, flavanones, flavanols, chalcones, and anthocyanidins (Figure 2), further grouped into categories like quercetin, kaempferol, myricetin, and fisetin [70,71]. Flavonoids have numerous health benefits, including anticancer [72], antibacterial [73], antioxidant, anti-inflammatory [20], anti-leishmanial [74], antidiabetic [75], Reno protective [76], cardioprotective [77], hepatoprotective [78], and neuroprotective properties, with studies on their pharmacological effects conducted on human and animal models [79-81].

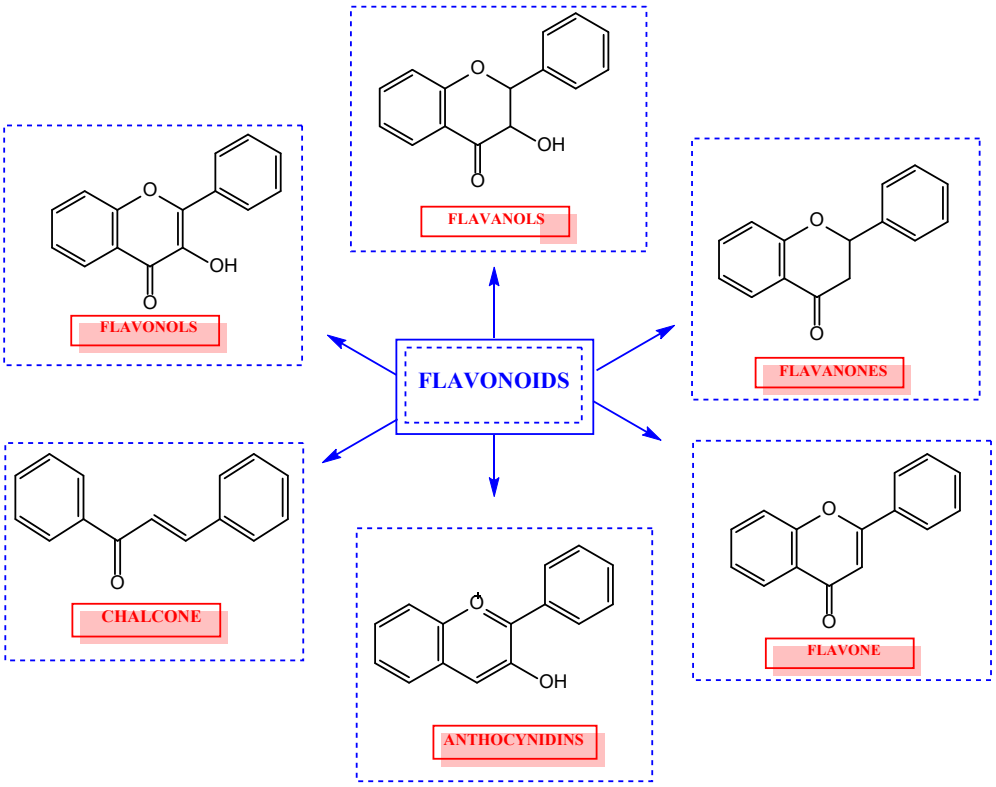

Figure 2: Structural Diversity Among Flavonoid Subclasses

Flavonols

Flavonol is a subclass of flavonoids that has particular substitutions on rings A, B, and C that give it a unique chemical structure [82]. Flavonoids may be found in many different types of food, mostly from plants [83]. Flavonoids like quercetin, rutin, kaempferol, morin, and gossypetin offer numerous therapeutic benefits, including antioxidant, anticancer, anti-inflammatory, cardioprotective, anti-apoptotic, renoprotective, and hepatoprotective properties [10, 84-87]. Quercetin is commonly used in several studies, mostly to investigate its ability to lower MDA levels and increase SOD and GSH functioning. Quercetin is commonly used in several studies, mostly to investigate its ability to lower MDA levels and increase SOD and GSH functioning [88]. Kaempferol has been demonstrated in scientific studies to have a preventive impact in lowering doxorubicin-induced liver, kidney, and cardiac damage [89,90]. Gossypium, a flavonol compound, protects kidneys from doxorubicin's nephrotoxic effects by restoring antioxidant enzyme activity, decreasing ROS and MDA levels, and restoring GSH Reductase activity in combination with doxorubicin [91].

Flavones

Luteolin, apigenin, diosmin, and chrysin belong to the subclass of flavones, which is also known as flavonoids. Among its many advantages are their hepatoprotective, renoprotective, cardioprotective, antioxidant, and anti-inflammatory properties [65,67,78,92-96]. Carbonyl reductase 3 is blocked by luteolin, preventing doxorubicin from being converted to doxorubicinol, according to studies [97]. Luteolin effectively treats doxorubicin-induced nephrotoxicity by reducing cell damage and impaired kidney and liver function, enhancing antioxidant enzymes, increasing IL-10 levels, and decreasing lipid peroxidation, among other factors. Its potent anti-inflammatory, anti-apoptotic, and antioxidant properties protect kidney cells, thereby reducing the risk of kidney and liver damage [98]. Glycosylated apigenin is often found with its tricyclic core structure joined to a sugar group either directly to a carbon atom (C-glycoside) or through a hydroxyl group (O-glycoside) [99]. Oxidative stress caused by hazardous drugs including doxorubicin, methotrexate, cyclophosphamide, and cisplatin has been demonstrated to be considerably reduced by apigenin [100-102]. These substances weaken the immune response by increasing the formation of ROS and depleting antioxidants [103]. The renoprotective action of apigenin was demonstrated by the reduction of proteinuria, the increase of Salb, the decrease of Scr and BUN, the increase of SOD and GSH activity, and the reduction of MDA, Caspase-1, Caspase-3, TNF-α, IL-6, IL-1β, and NLR family Pyrin domain containing 3 (NLRP3) for the kidney healing process.[65] Diosmin, also known as diosmetin 7-O-rutinoside, is a naturally occurring flavonoid glycoside [104]. Diosmin has shown a variety of biological characteristics, as shown by several in vitro and in vivo studies [105]. Diosmin reduces the synthesis of pro-inflammatory cytokines by inhibiting the NF-κB pathways and decreasing the expression of T Cell Receptors (TCRs [106]. As a result, it helps prevent damage to the kidneys and liver tissues brought on by inflammation. Diosmin's renoprotective effects have been demonstrated in studies on live animals using dosages of 100 mg/kg and 200 mg/kg [107].

Flavanones

Flavanones, a subclass of flavonoids distinguished by the saturation of their C rings, including naringenin and hesperidin. The antioxidant qualities and capacity to eradicate free radicals of naringenin and hesperidin have been thoroughly examined using a variety of testing techniques [108]. Hesperidin and naringenin are two substances that have a variety of biological actions, such as immunomodulatory, anti-inflammatory, hepatoprotective, cardioprotective, renoprotective,

antioxidant, and anti-cancer properties [108-112]. In mice, naringenin and hesperidin treatment was shown to reduce oxidative stress brought on by elevated ROS production and antioxidant depletion from doxorubicin. According to experimental data, giving 100 mg/kg of naringenin can lower the amount of ROS caused by doxorubicin by boosting the activity of antioxidants like GSH, GPx, SOD, and CAT and lowering the inflammatory response that includes TNF-α, IL-1β, IL-6, Transforming Growth Factor-β (TGF-β), and prostaglandin-E2 (PGE-2) while blocking NF-κB and NO to safeguard kidney health [113]. Hesperidin, when administered at a dose of 50 mg/kg, reduced urea, Scr, uric acid, Sodium, and Potassium levels, while increasing antioxidant activity, indicating its crucial role in protecting vital organs from oxidative stress induced by doxorubicin at 10 mg/kg [114].

Table 1: Overview of Flavonoids Exhibiting Renoprotective Activity in Doxorubicin-Treated Animal Models.

Compound	Study design	Flavonoid dose	Doxorubicin dose	Duration	Parameters	References
Apigenin	*In vivo (BALB/c mice)*	125 mg/kg 250 mg/kg 500 mg. kg (P. O for 17 d)	11.5 mg/kg (I. V tail vein to for a single injection)	17 days	↓Proteinuria, ↑Salb, ↓Scr, ↓BUN, ↑SOD, ↓MDA, ↑GSH, ↓Caspase-1, ↓Caspase-3, ↓TNF-α, ↓IL-6, IL-1β, ↓NLRP3	[65]
Anthocyanidins	*In vivo (New Zealand rabbits)*	75 mg/kg 150 mg/kg (O. S once daily for 4 w)	1.5 mg/kg (I. V for once weekly for 5 w)	9 weeks	↑SOD, ↑CAT, ↓LPO	[136]
Chrysin	*In vivo (Rats Wistar)*	40 mg/kg 80 mg/kg (P. O for 16 d)	40 mg/kg (I. P. injection of a single dose)	16 days	↓Scr, ↓BUN, ↑SOD, ↑CAT, ↑GSH, ↑GPx, ↑GR, ↓MDA	[147]
Diosmin	*In vivo (Wistar rats)*	100 mg/kg 200 mg/kg (P. O for 18 d)	20 mg/kg (I. P. injection of a single dose)	18 days	↓BUN, ↓Scr, ↑Salb, ↓MDA, ↑GSH, ↑CAT, ↑SOD, ↑IL-10, ↓IL-6, ↓NF-κB p65, ↓iNOS, ↓Caspase-3, ↓BAX,	[107]

					↑BCL-2, ↓TNF-α, ↓NOX-4	
Gossypetin	*In vivo (Sprague-dawley rats)*	30 mg/kg (P. O for 30 d)	3 mg/kg (I. P. injection of a single dose)	30 days	↑GPx, ↑SOD, ↑CAT, ↑GST, ↓ROS, ↓MDA, ↓urea, ↓Scr, ↑CrCl, ↓KIM-1, ↓NGAL, ↓NF-κB, ↓TNF-α, ↓IL-1β,	[91]
Isoliquiritigenin	*In vivo (Wistar rats)*	25 mg/kg (P. O for 20 d)	15 mg/kg (I. P. injection of a single dose)	3 weeks	↑Final body weights, ↓urea, ↑GFR, ↓Scr, ↑CrCl, ↑Salb, ↓urea, ↓Alb/Ucr ratio, ↓ROS/RNS, ↓MDA, ↑GSH, ↑SOD.	[127]
Kaempferol	*In vivo* (Wistar rats)	200 mg/kg (P. O for 20 d)	15 mg/kg ((I. P. injection of a single dose on th	20 days	↓Body weights, ↓Cr, ↓CrCl, ↑GSH, ↑SOD, ↑NRF2, ↓NF-κB p65, ↓MDA, ↓TNF-α, ↓IL-6, ↓ROS	[146]
Luteolin	*In vivo (Wistar rats)*	50 mg/kg 100 mg/kg (P. O for 14 d)	2 mg/kg (I. P injection every other day for 6 d)	14 days	↓LDH, ↓AST, ↓ALT, ↓ALP, ↓GGT, ↓Scr, ↑GPx, ↑GST, ↑GSH, ↑SOD, ↑CAT, ↑Total Sulfhydryl Group (TSH), ↓LPO, ↓RONS,	[98]
Morin	*In vivo* (Wistar rats)	50 mg/kg 100 mg/kg (P. O for 10 d)	40 mg/kg (I. P injection every other day for 8 d)	10 days	↑GSH, ↑MDA, ↑SOD, ↑CAT, ↑GPx, ↓Scr, ↓urea, ↓TNF- α, ↓IL-1β, ↓NF-kβ, ↓BCL-2, ↓AQP 2	[143]
Proanthocyanidins	*In vivo (Swiss albino rats)*	200 mg/kg (P. O for 21 d)	7.5 mg/kg (I. V tail vein for a single injection)	3 weeks	↑Final body weight, ↓absolute kidney weight, ↓Urea, ↓Scr, ↑Salb, ↓MDA, ↑SOD,	[119]

					↑GSH, ↓COX-2, ↓NO, ↓Caspase-3, ↓TNF-α	
Quercetin	*In vivo* (Wistar rats)	10 m/kg/d (Per Os (P. O) for 14 d)	15 mg/kg (Intraperitoneal (I. P) injection on day 7)	2 weeks	↓Kidney Index, ↓BUN, ↓Scr, ↓MDA, ↓NO, ↓GSH, ↓CAT, ↓TNF-α, ↓IL-1β, ↓inducible NOS, ↓Caspase-3	[137]
Quercetin	*In vivo* (Wistar rats)	50 mg/kg/d (P. O for five weeks)	2 mg/kg (I. P injections twice a week for five weeks)	5 weeks	↓BUN, ↓Scr, ↑GSH, ↓LPO, ↓MDA, ↑GPx, ↑GST, ↑SOD	[141]
Rutin	*In vivo* (Wistar rats)	50 mg/kg (P. O for five weeks)	2 mg/kg (I. P injections twice a week for five weeks)	5 weeks	↓BUN, ↓Scr, ↑GSH, ↓LPO, ↓MDA, ↑GPx, ↑GST, ↑SOD	[141]

Flavanols

Flavonols, also known as flavan-3-ols, are a subclass of flavonoids, which are plant substances with possible health benefits and antioxidant qualities. Foods including fruits, vegetables, tea, and chocolate frequently contain them [115]. Epicatechin, catechin, epigallocatechin gallate, theaflavins, and procyanidins are examples of flavanols that have been studied for their renoprotective, cardioprotective, and hepatoprotective potential, underscoring their wider health benefits [116,117]. Flavanols are recognized for their antioxidant, anti-inflammatory, and possibly anticancer quality [118]. Apoptosis, inflammation, oxidative stress, and DNA damage in renal tissue are the ways that doxorubicin causes nephrotoxicity. Proanthocyanidin compounds are flavanols that have been shown to decrease doxorubicin-induced nephrotoxicity in mice by decreasing oxidative stress biomarkers like MDA, raising antioxidant enzymes like SOD and GSH, and decreasing inflammatory and apoptotic markers like NO, caspase-3, and Cyclooxygenase-2 (COX-2) in kidney tissue [119].

Chalcones

Many plant flavonoids and iso flavonoids are biogenically derived from chalcones, a subclass of flavonoids having a C6-C3-C6 structure [120]. Phloretin, butein, isoliquiritigenin, Lico chalcone E, xanthohumol, and chalcone aringenin are a few examples of bioactive chalcone chemicals that are recognized for their biological actions [121,122]. Chalcones have a wide range of biological uses, such as neuroprotective [123], anticancer [124], hepatoprotective [125], antioxidant, anti-inflammatory, and renoprotective properties [126]. Scientifically proven to be an effective chalcone,

isoliquiritigenin enhances kidney function by lowering urea and urine creatinine (UCR) levels, raising GFR, improving creatinine clearance (CrCl), raising Salb levels, lowering ROS/RNS and MDA levels to guard against oxidative stress, and raising GSH and SOD activity [127].

Anthocyanins

Plant pigments that dissolve in water and are members of the flavonoid group are called anthocyanins [128]. A variety of fruits and vegetables include the anthocyanin subclasses delphinidin, petunidin, malvidin, cyanidin, peonidin, and pelargonidin [129]. Furthermore, these substances provide a variety of plants striking red, purple, blue, and black hues [130]. They have specific anti-inflammatory, anti-cancer, anti-apoptotic, renoprotective, hepatoprotective, and cardioprotective antioxidant qualities [131-135]. It has been demonstrated that giving anthocyanins at dosages of 75 mg/kg and 150 mg/kg protects the kidneys as a renoprotective drug in New Zealand rabbits under oxidative stress brought on by doxorubicin induction, raising SOD and CAT activity and lowering LPO levels [136].

3. CONCLUSION

Doxorubicin-induced nephrotoxicity arises through multiple interconnected pathways, including impaired antioxidant defenses, reduced mitochondrial function in renal tissues, and enhanced inflammatory responses. Despite extensive research, a comprehensive understanding of the precise molecular mechanisms involved remains incomplete, highlighting the need for continued investigation. Flavonoids, including quercetin, chrysin, rutin, kaempferol, morin, luteolin, apigenin, hesperidin, naringenin, diosmin, and anthocyanins, have demonstrated significant nephroprotective effects by attenuating oxidative stress, inhibiting lipid peroxidation, stabilizing mitochondrial membranes, and reducing apoptosis. These findings underscore the therapeutic potential of flavonoids as adjunctive agents in mitigating doxorubicin-induced renal damage. Future studies should further explore novel flavonoid-based strategies and their molecular targets to enhance renal protection and improve the safety profile of chemotherapeutic regimens.

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