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Review Article

RENOPROTECTIVE POTENTIAL OF FLAVONOIDS-RICH AGAINST DOXORUBICIN-INDUCED IN ANIMAL MODELS: A REVIEW

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ABSTRACT

Cancer significantly impacts human health, affecting one in five people during their lifetime. While chemotherapeutic agents like doxorubicin are crucial in treating various cancers, they are also associated with severe side effects, including nephrotoxicity. This review examines the renoprotective potential of flavonoids against doxorubicin-induced renal damage in animal models. Doxorubicin works by intercalating Deoxyribo Nucleic Acid (DNA) and making Reactive Oxygen Species (ROS), which cause apoptosis and the death of cells. A thorough literature analysis was done to collect relevant papers on the impact of flavonoid-rich therapies as renoprotective agents against doxorubicin-induced nephrotoxicity. Databases such as Google Scholar, Scopus, PubMed, Springer, Wiley Online Library, and ScienceDirect were searched using keywords including "flavonoids, doxorubicin, renoprotective, nephrotoxicity, and animal model," focusing on publications from 2014 to 2024. Flavonoids are diverse polyphenolic compounds in many plants with significant pharmacological properties such as antioxidant, anti-inflammatory, and anticancer effects. This review highlights the renoprotective potential of flavonoids like quercetin, rutin, kaempferol, morin, luteolin, apigenin, hesperidin, naringenin, diosmin, and anthocyanins. These compounds reduce renal toxicity through mechanisms that decrease ROS, lipid peroxidation, mitochondrial permeability, and apoptosis.

Keywords: Doxorubicin, Nephrotoxicity, Renoprotective, Flavanoids

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INTRODUCTION

Cancer has become one of the worst illnesses for humans, with one in every five men and women having cancer at some point in their lives. Projections for the year 2022 indicate that there will be approximately 20 million instances of cancer, and out of those, nearly 10 million individuals are expected to die as a result [1]. Chemotherapeutic agents are chemical medications that kill and suppress cancer cells and cell proliferation, preventing cancer cells' unchecked development and proliferation [2]. Doxorubicin is a potent chemotherapeutic agent that successfully targets and cures several types of cancer. Doxorubicin is classified as an anthracycline treatment derived from the bacterium *Streptomyces peucetius* and has a close relationship with antibiotic drugs [3, 4].

Doxorubicin is employed in treating numerous tumor types in cancer patients, delivering therapeutic advantages through a complex mechanism involving multiple cell death routes, including apoptosis, pyroptosis, ferroptosis, and necroptosis [5–7]. In addition, doxorubicin exerts its effects on cancer cells in many ways, such as intercalating into the DNA double helix and generating free radicals that can damage cell membranes, DNA molecules, and proteins by interfering with topoisomerase II-mediated DNA repair. The latter step occurs when doxorubicin is oxidized to form an unstable metabolite called semiquinone, which is then converted back into doxorubicin, producing ROS [8, 9]. Doxorubicin exhibits notable anticancer activity, but its long-term administration as a chemotherapeutic agent can lead to adverse effects and subsequent issues, specifically hepatotoxicity, cardiotoxicity, and nephrotoxicity [10–12]. Doxorubicin can cause nephrotoxic effects, which can be identified through glomerular pathology and the appearance of clinical symptoms related to nephrotic syndrome [13]. The kidneys play an essential function in the human body by eliminating waste chemicals, maintaining homeostasis, and regulating acid-base balance. Disruption or toxic exposure to the glomeruli and tubules significantly affects the body's metabolic function, especially regarding the side effects of chemotherapeutic agents. That can result in inadequate renal function in the filtration of chemotherapy medications, increasing the likelihood of renal failure [14, 15].

Certain groups of people often utilize medicinal plants in their traditional medicine practices [16]. Natural plants contain many secondary metabolite compounds, such as flavonoids, which are diverse polyphenolic compounds found abundantly in various plant parts such as flowers, leaves, stems, and fruits [17]. In addition, flavonoids have various pharmacological benefits, including anti-inflammatory, anticancer, antitumor, neuroprotective, antioxidant, antiviral, antibacterial, and anti-angiogenic [18–20]. Flavonoids are classified into several classes, including flavonols, flavones, flavanones, flavanols, isoflavonoids, and anthocyanidins [21]. These compounds effectively enhance the expression of protective enzymes such as Catalase (CAT), Glutathione (GSH), Superoxide Dismutase (SOD), GSH Peroxidase (GPx), and Nuclear factor erythroid 2-Related Factor 2 (NRF2) [22, 23]. Moreover, flavonoids suppress the expression of pro-apoptotic proteins such as Cytochrome C (Cyt C), B-Cell Lymphoma 2(BCL-2)-associated X protein (BAX), and caspase-3, caspase-7 and caspase-9 while also lowering 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) [4, 24]. This study aims to review the renoprotective potential of flavonoids against renal damage induced by doxorubicin in experimental animal models. This literature review was performed to gather pertinent information on the impact of flavonoid-rich substances as a renoprotective drug in animal models induced by doxorubicin. Studies conducted on the keywords "flavonoids, doxorubicin, renoprotective, nephrotoxicity, and animal model" were collected from globally renowned databases such as Google Scholar, Scopus, PubMed, Springer, Wiley Online Library, and ScienceDirect. The primary emphasis is on publications published between 2014 and 2024, covering the past 10 years. However, a few articles from before 2013 have been included to ensure no significant insights on flavonoids are overlooked. In order to ensure the completeness of this narrative, we also considered the pertinent references provided in these publications.

Mechanism of doxorubicin action

Doxorubicin is widely utilized as a chemotherapeutic agent. Doxorubicin is classified as an anthracycline treatment derived from *Streptomyces peucetius* bacteria and is closely related to antibiotic drugs [3, 25]. However, the precise mechanism by which doxorubicin exerts its effects remains uncertain [8]. Some sources explain that the mechanism of doxorubicin, as a cancer chemotherapy drug, works in a complex manner with several

mechanisms of action, including DNA Intracellularly, Topoisomerase II Inhibition, and ROS production [26].

The interaction of doxorubicin with DNA is referred to as intercalation [27]. Doxorubicin, through a passive diffusion process, enters the nucleus of cancer cells through the cell membrane by forming doxorubicin complexes in the form of 20s proteasome subunits and enters between DNA bases, thus inhibiting critical macromolecular synthesis processes [28]. Doxorubicin has a structure of aglyconic and daunosamine groups that result in interactions between doxorubicin and Ribo Nucleic Acid (RNA) and DNA, causing stretching and breaking of DNA double chains and inhibiting replication and transcription of cancer cell DNA. In addition, the intercalation of doxorubicin with DNA results in the inhibition of the activity of the enzyme topoisomerase II, which has the role of opening and closing DNA strands during the process of DNA replication and repair, so that the action of doxorubicin that paralyzes topoisomerase II results in inhibition of normal DNA replication, preventing the formation of accurate DNA copies and stopping the growth of cancer cells [29]. Doxorubicin-induced inhibition of the topoisomerase II enzyme, which involves DNA replication, may contribute to the production of ROS [8].

Doxorubicin can trigger the production of ROS through several mechanisms in cancer cells [30]. One of the main mechanisms is the conversion of doxorubicin to semiquinone doxorubicin by mitochondrial Nicotinamide Adenine Dinucleotide Phosphate (NADPH) oxidase within the mitochondria, which then generates Superoxide Anion (O_2-) as a by-product. In addition, doxorubicin interacts with the Nitric Oxide Synthase (NOS) enzyme, which uses NADPH as a reductant to produce Nitric Oxide (NO) from L-arginine in the presence of molecular Oxygen (O_2). When levels of L-arginine or the cofactor BH4 are limited, NOS undergoes uncoupling, producing superoxide rather than NO. ROS generated by doxorubicin causes direct damage to the DNA of cancer cells, including damage to DNA bases and sugar-phosphate backbone, which can lead to apoptosis if not repaired [31].

Doxorubicin also induces damage to the mitochondrial membrane by interacting with cardiolipin, a lipid in the inner mitochondrial membrane, increasing ROS production and damaging mitochondrial structure, ultimately causing apoptosis in cancer cells. In addition, Doxorubicin increases the expression of pro-apoptotic proteins such as BAX so that it can decrease the expression of anti-apoptotic proteins such as BCL-2, releases Cyt C from mitochondria to the cytosol and activates caspase-3, a key enzyme in the apoptotic pathway. Through this mechanism, excessive ROS production in cancer cells causes oxidative stress, which damages DNA, proteins, and lipids, thereby triggering cellular mechanisms that cause cell death and inhibit the growth and spread of cancer cells [32, 33].

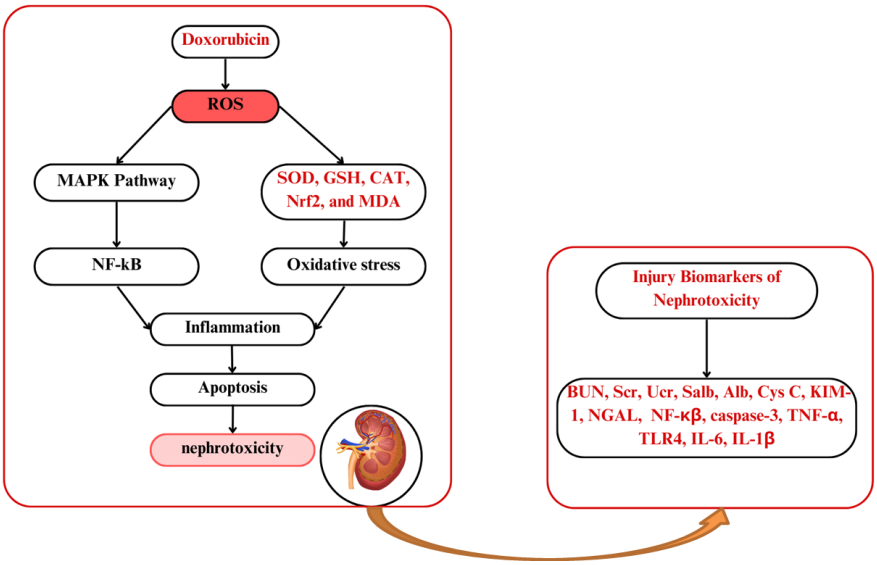

Fig. 1: Doxorubicin-induced ROS-induced oxidative stress causes nephrotoxicity [34]

Mechanisms of ROS generation in doxorubicin-induced kidney injury

The administration of doxorubicin has been shown to induce the generation of ROS inside the cytosol and mitochondria of the kidney [35, 36]. Moreover, the enzyme NADPH Oxidase (NOXs) is in the plasma membrane [37]. It could enhance the production of ROS. Doxorubicin breaks down to yield doxorubicin-semiquinone, rapidly oxidizing to produce O_2-radicals by converting molecular O_2 [34]. Unfortunately, the presence of NO greatly increases the responsiveness of molecular O_2, resulting in the formation of Peroxynitrite (ONOO-) [38]. The removal of ROS is usually facilitated by internal antioxidants like SOD or exogenous antioxidants like flavonoids, which produce Hydrogen Peroxide (H_2O_2) [39, 40]. The Fenton reaction involves the direct conversion of H_2O_2 into Hydroxyl Radicals (OH) in the presence of Iron (Fe^{2+}) [41]. Conversely, the administration of a substantial quantity of doxorubicin results in a significant rise in the generation of ROS.

Doxorubicin induces substantial elevations in ROS production, leading to evident oxidative damage. Oxidative stress can trigger the breakdown of lipids in cell membranes, decrease Adenosine Triphosphate (ATP) levels, produce ONOO-, enhance the vulnerability of ryanodine receptors, and ultimately result in mitochondrial dysfunction. Consequently, an excessive amount of Calcium (Ca) is released into the cytosol, causing harm to both the cytosol and the mitochondria [6, 42]. Doxorubicin-induced ROS-induced oxidative stress triggers inflammatory responses and apoptosis in the kidneys, activating pathways like Mitogen-Activated Protein Kinase (MAPK) and NF-κB, which can be detected by biomarkers such as IL-6, IL-1β, TNF-α, Kidney Injury Molecule-1 (KIM-1), Neutrophil Gelatinase-Associated Lipocalin (NGAL), and Cystatin C (Cys C), ultimately leading to nephrotoxicity as shown in fig. 1 [34].

Injury biomarkers of nephrotoxicity

Oxidative stress generated by ROS is the primary factor responsible for kidney damage from doxorubicin treatment. The initial diagnostic test for chronic kidney injury evaluates elevated levels of Blood Urea Nitrogen (BUN), Serum Creatinine (Scr), Serum Albumin (Salb), and the presence of pathological kidney cell destruction [43, 45]. BUN and SCR tests are imprecise kidney function indices due to their vulnerability to several renal and non-renal factors unrelated to kidney function. In addition, nephrotoxicity in the kidney can be

identified by using indicators of acute renal injury, such as proteinuria Cys C [45, 46].

Reduced levels of antioxidant gene biomarker tests, such as CAT, SOD, GSH, and NRF2, along with elevated levels of Malondialdehyde (MDA), can serve as compelling evidence that nephrotoxicity is a result of oxidative stress [47–50]. Damage to the proximal tubule leads to an elevate transmembrane glycoprotein biomarker KIM-1 production in renal tubular cells [51–53]. An elevated NGAL is a reliable marker for kidney injury from toxins exposure [54]. Elevated levels of inflammatory factors, including NF-κβ, caspase-3 [55], Toll-Like Receptor 4 (TLR4) [56], TNF-α [57], MAPK [58], IL-6, and IL-1β, can lead to inflammation in kidney tissue [24, 59, 60].

Kidney tissue disorders due to doxorubicin

Administering doxorubicin can have detrimental effects by inducing an accumulation of unpaired electrons within proteins in the renal tissue. This can result in changes to the structure and function of the kidney tubules and glomeruli, as well as the manifestation of clinical symptoms related to nephrotic syndrome. Doxorubicin induction can lead to the development of nephrotic syndrome by interfering with normal mitochondrial function, reducing the activity of complex I and complex IV, impeding nephron formation, and initiating glomerulosclerosis [61–63]. The primary role of renal tubule cells is to serve as the kidney's filtration and absorption mechanism due to their major structural components. Kidney tubular injury or apoptosis can hasten the death of nephrons, exacerbating fibrous inflammation [64].

The administration of doxorubicin leads to specific changes in the structure of kidney tissue. These changes include the formation of vacuoles in the endothelial cells of the glomeruli bundles, congestion and swelling of blood vessels in the cortical stroma, an increase in the growth of fibroblastic cells, and localized inflammation between the cortical glomeruli and tubules. In addition, there might be localized hemorrhaging and scarring between the tubules [45, 65].

Flavonoids

Several plants produce flavonoids, phenolic compounds, and bioactive secondary metabolites, which may be found in various parts of plants, such as roots, leaves, seeds, and stems [66–68]. Flavonoid molecules have a structural composition comprising 15 carbon atoms (C6-C3-C6) organized into two benzene rings (A and B) linked by a three-carbon bridge. Flavonoid compounds are categorized according to the level of carbon ring oxidation, level of saturation, and chemical structure of the molecule [69]. Flavonoid molecules may be classified into many subclasses, such as flavonols, flavones, flavanones, flavanols, chalcones, and anthocyanidins (fig. 2). These subclasses are further grouped into categories like quercetin, kaempferol, myricetin, and fisetin [70, 71]. Flavonoids have been widely used as agents with anticancer [72], antibacterial [73], antioxidants, anti-inflammatory [20], anti-leishmanial [74], antidiabetic [75], renoprotective [76], cardioprotective [77], hepatoprotective [78], neuroprotective, and cytotoxic properties [79]. Moreover, investigations on the pharmacological effects of flavonoids have been conducted using both human and animal models [80, 81].

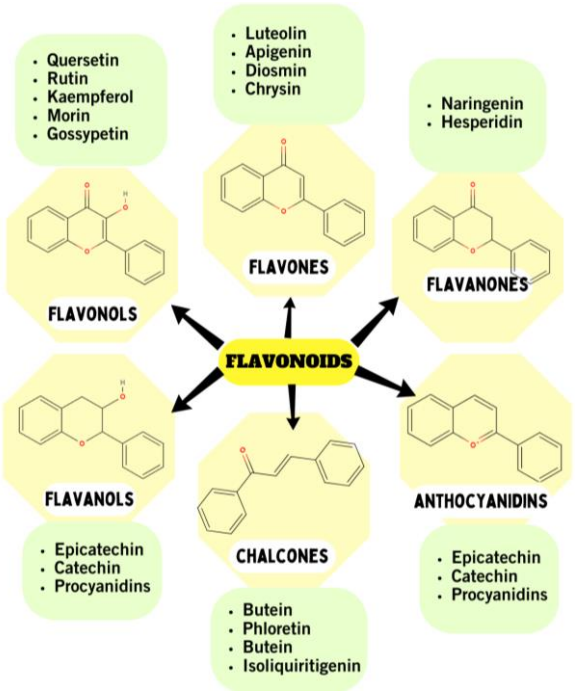

Fig. 2: Structure of flavonoid subclasses [82, 83]

Flavonols

Flavonol, a subclass of flavonoids, features a distinctive chemical structure with specific substitutions on rings A, B, and C. Flavonoids are widely present in various food sources, primarily from plants [82, 83]. The flavonoids mentioned, such as quercetin, rutin, kaempferol, morin, and gossypetin, have various therapeutic benefits, including antioxidant, anticancer, anti-inflammatory, cardioprotective, anti-apoptotic, renoprotective, and hepatoprotective properties [10, 84-87]. Quercetin is frequently employed in many research studies, mostly to examine its capacity to decrease MDA levels and enhance the activity of SOD and GSH [88]. Scientific research indicates that kaempferol has been shown to have a protective effect in reducing doxorubicin-induced damage to the heart, kidneys, and liver [89, 90]. In addition, it has been proven that the Gossypetin compound, which is part of the flavonols, has a protective effect on the kidneys against the nephrotoxic effects of doxorubicin by showing restoration of the activity of antioxidant enzymes such as GSH Reductase (GR), GSH-S-Transferase (GST), GPx, SOD, CAT, as well as GSH, as well as decreased levels of ROS and MDA in the group treated with combination Gossypetin and doxorubicin compared with the group exposed only to doxorubicin [91].

Flavones

Luteolin, apigenin, diosmin, and chrysin are members of the flavones subclass categorized as flavonoids. They exhibit several benefits, including anti-inflammatory, antioxidant, renoprotective,

cardioprotective, and hepatoprotective characteristics [65, 67, 78, 92–96]. According to reports, luteolin has been shown to block carbonyl reductase 3, which prevents the conversion of doxorubicin to doxorubicinol [97]. Luteolin effectively treats doxorubicin-induced nephrotoxicity by reducing Scr, Lactate Dehydrogenase (LDH), Gamma-Glutamyl Transferase (GGT), Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), and Alkaline Phosphatase (ALP) levels indicating cell damage and impaired kidney and liver function, while enhancing antioxidant enzymes like GPx, GST, GSH, SOD, and CAT, increasing IL-10 levels, and decreasing Lipid Peroxidation (LPO), Reactive Oxygen/Nitrogen Species (RONS), Xanthine Oxidase (XO), Myeloperoxidase (MPO), NO, TNF-α, IL-1β, caspase-9, and caspase-3 levels, with its potent anti-inflammatory, anti-apoptotic, and antioxidant properties protecting kidney cells [98].

Apigenin is generally found in a glycosylated form, where its tricyclic core structure is attached to a sugar group via a hydroxyl group (O-glycoside) or directly to a carbon atom (C-glycoside) [99]. Apigenin has been shown to significantly reduce oxidative stress induced by toxic agents such as cisplatin, methotrexate, doxorubicin, and cyclophosphamide [100–102]. These agents trigger increased ROS production and antioxidant depletion, impairing the immune response [103]. Apigenin was proven to have a renoprotective effect by reducing proteinuria, increasing Salb, decreasing Scr and BUN, increasing SOD and GSH activity, and reducing levels of MDA, Caspase-1, Caspase-3, TNF-α, IL-6, IL-1β, and NLR family Pyrin domain containing 3 (NLRP3) in the kidney healing process [65].

Diosmin, often called diosmetin 7-O-rutinoside, is a flavonoid glycoside naturally found in nature [104]. Diosmin has demonstrated diverse biological properties, as evidenced by several *in vitro* and *In vivo* investigations [105]. Diosmin has anti-inflammatory effects by inhibiting the NF-κB pathways and reducing the expression of T Cell Receptors (TCRs), hence lowering the production of pro-inflammatory cytokines [106]. Therefore, it assists in controlling inflammation-induced harm to the kidneys and liver tissues. Studies on live animals utilizing doses of diosmin at 100 mg/kg and 200 mg/kg have yielded evidence supporting diosmin's renoprotective effects [107].

Flavanones

Naringenin and hesperidin are flavanones, a subclass of flavonoids characterized by the saturation of their C rings. A comprehensive study has investigated naringenin and hesperidin's antioxidant properties and ability to eliminate free radicals using various testing methods [108]. These two compounds, hesperidin and naringenin, exhibit various biological activities, including antioxidant, anti-cancer, immunomodulatory, anti-inflammatory, hepatoprotective, cardioprotective, and renoprotective effects [108–112]. The administration of naringenin and hesperidin to mice was demonstrated to be beneficial in lowering oxidative stress caused by increased ROS generation and antioxidant depletion generated by doxorubicin, as detailed in table 1.

Experimental evidence shows that administering a dose of 100 mg/kg naringenin can reduce the level of ROS induced by doxorubicin by increasing the activity of antioxidants such as GSH, GPx, SOD, and CAT and reducing the inflammatory response involving TNF-α, IL-1β, IL-6, Transforming Growth Factor-β (TGF-β), and Prostaglandin-E2 (PGE-2) while inhibiting NF-κB and NO to protect kidney health [113]. In addition, administering a dose of 50 mg/kg, hesperidin was also shown to reduce levels of urea, Scr, uric acid, Sodium (Na+), and Potassium (K+), as well as increasing the activity of antioxidants such as GSH, GPx, and GST, indicating its important role in protecting vital organs from damage caused by oxidative stress induced by doxorubicin at a dose of 10 mg/kg [114].

Table 1: Renoprotective activity of flavonoids against doxorubicin-induced nephrotoxicity

Compound	Study design	Flavonoid dose	Doxorubicin dose	Duration	Parameters	References
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 W	↓Kidney Index, ↓BUN, ↓Scr, ↓MDA, ↓NO, ↓GSH, ↓CAT, ↓TNF-α, ↓IL-1β, ↓inducible NOS, ↓Caspase-3	[137]
Quercetin	*In vivo* (Wistar rats)	2 mg/kg/d (P. O for 7 d)	10 mg/kg (Intravenous (I. V) injection on day 5)	1 W	↓BUN, ↓Scr, ↓MDA, ↑GSH, ↓K+, ↓Aspartate Amino Transferase (AST), ↓LDH, ↓Thiobarbituric Acid Reactive Substances (TBARS)	[138]
Quercetin	*In vivo* (Wistar rats)	10 mg/kg/d (P. O for 10 w)	1.8 mg/kg (I. P injection once every three weeks, for ten weeks)	10 w	↓MDA, ↑GSH, ↓GPx, ↑CAT, ↓SOD	[139]
Quercetin	*In vivo* (Sprague–dawley rats)	50 mg/kg/d (P. O for 15 d)	2.5 mg/kg (I. P injections three times a week, for two weeks)	4 w	↓BUN, ↓Scr, ↓Total Cholesterol (TC), ↓Triglycerides (TG), ↓Low-Density Lipoprotein Cholesterol (LDL-C), ↑High-Density Lipoprotein Cholesterol (HDL-C), ↑Total Protein levels, ↓NO, ↓TNF-α, ↓MPO, gene expression (↓desmin, ↓vimentin, ↓connexin 43, ↓nestin)	[140]
Quercetin	*In vivo* (Wistar rats)	10 mg/kg/d 100 mg/kg/d (I. P on 21 d)	18 mg/kg (I. P during the last 3 d of treatment)	3 w	↓BUN, ↓Scr, ↓NO, ↓TNF-α, ↓IL-6, ↑Technetium-99m Dimercaptosuccinic Acid ([99mTc]Tc-DMSA)	[4]
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 w	↓BUN, ↓Scr, ↑GSH, ↓LPO, ↓MDA, ↑GPx, ↑GST, ↑SOD	[141]
Quercetin	*In vivo* (SPF C57BL/6 mice)	25 mg/kg 50 mg/kg (I. V. tail vein injections twice a week for 12 w)	10.5 mg/kg (I. V tail vein for a single injection)	12 w	↓Scr, ↑ Ucr, ↑GFR, ↓urea, ↓Urine albumin (Alb), ↓BAX, ↑BCL-2, ↓Cyt-C, ↓Angil, ↓TNF-α, ↓iNOS, ↓IL-1β,↑IL-4, ↓IL-6, ↑IL-10, ↑AKT1, ↑Raf, ↑MEK, ↑p-ERK/ERK, ↑p-ERK/β-actin	[142]
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 w	↓BUN, ↓Scr, ↑GSH, ↓LPO, ↓MDA, ↑GPx, ↑GST, ↑SOD	[141]
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 d	↑GSH, ↑MDA, ↑SOD, ↑CAT, ↑GPx, ↓Scr, ↓urea, ↓TNF-α, ↓IL-1β, ↓NF-kβ, ↓BCL-2, ↓AQP 2	[143]
Morin	*In vivo* (Wistar rats)	100 mg/kg (P. O for 7 d)	40 mg/kg (I. P. injection of a single dose on the 15th d)	1 w	↓Uric acid, ↓urea, ↓Scr, ↓MDA, ↓NO, ↑SOD, ↑CAT, ↑GSH, ↑GPx, ↓Kidney weight	[144]
Kaempferol	*In vivo* (BALB/c mice)	10 mg/kg (P. O for 17 d)	11.5 mg/kg (I. V injection of a single dose)	17 d	↓Weight loss, ↓ratio of kidney weight to body weight, ↓BUN, ↓Src, ↓ Alb/Ucr ratio, ↓renal tubular injury score, ↓caspase-3, ↑BCL-2/BAX, ↓p53, ↑SOD, ↑SOD2, ↑GSH, ↑CAT, ↓MDA, ↓MAPK	[145]
Kaempferol	*In vivo* (Wistar rats)	200 mg/kg (P. O for 20 d)	15 mg/kg ((I. P. injection of a single dose on the 10 d)	20 d	↓Body weights, ↓Cr, ↓CrCl, ↑GSH, ↑SOD, ↑NRF2, ↓NF-κB p65, ↓MDA, ↓TNF-α, ↓IL-6, ↓ROS	[146]

Compound	Study design	Flavonoid dose	Doxorubicin dose	Duration	Parameters	References
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 d	↑GPx, ↑SOD, ↑CAT, ↑GST, ↓ROS, ↓MDA, ↓urea, ↓Scr, ↑CrCl, ↓KIM-1, ↓NGAL, ↓NF-κB, ↓TNF-α, ↓IL-1β, ↓IL-6, ↓COX-2, ↓BAX, ↑BCL-2, ↓Caspase-9, ↓Caspase-3.	[91]
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 d	↓Scr, ↓BUN, ↑SOD, ↑CAT, ↑GSH, ↑GPx, ↑GR, ↓MDA	[147]
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 d	↓LDH, ↓AST, ↓ALT, ↓ALP, ↓GGT, ↓Scr, ↑GPx, ↑GST, ↑GSH, ↑SOD, ↑CAT, ↑Total Sulfhydryl Group (TSH), ↓LPO, ↓RONS, ↓XO, ↓NO, ↓MPO, ↓TNF-α, ↓IL-1β, IL10, ↓Caspase-9, ↓Caspase-3	[98]
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 d	↓Proteinuria, ↑Salb, ↓Scr, ↓BUN, ↑SOD, ↓MDA, ↑GSH, ↓Caspase-1, ↓Caspase-3, ↓TNF-α, ↓IL-6, IL-1β, ↓NLRP3	[65]
Rutin and Hesperidin	*In vivo* (Wistar rats)	50 mg/kg (P. O for 3 times per week for 3 w)	25 mg/kg (I. P injection for 3 times per week 2 w)	5 w	↓Urea, ↓Scr, ↓Uric acid, ↓Na+, ↓K+, ↑GSH, ↑GPx, ↑GST	[114]
Naringenin	*In vivo* (Wistar rats)	50 mg/kg 100 mg/kg (P. O for 17 d)	10 mg/kg (I. P. injection of a single dose)	21 d	↓BUN, ↓Scr, ↓LDH, ↑GSH, ↓Oxidized GSH (GSSG), ↑GPx, ↓GR, ↑SOD, ↓H_2O_2, ↑CAT, ↓ROS, ↓KIM-1, ↓MDA, ↓NO, ↓NF-κβ, ↓TNF-α, ↓IL-1β, ↓IL-6, ↓TGF-β, ↓PGE-2	[113]
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 d	↓BUN, ↓Scr, ↑Salb, ↓MDA, ↑GSH, ↑CAT, ↑SOD, ↑IL-10, ↓IL-6, ↓NF-κB p65, ↓iNOS, ↓Caspase-3, ↓BAX, ↑BCL-2, ↓TNF-α, ↓NOX-4	[107]
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 w	↑Final body weight, ↓absolute kidney weight, ↓Urea, ↓Scr, ↑Salb, ↓MDA, ↑SOD, ↑GSH, ↓COX-2, ↓NO, ↓Caspase-3, ↓TNF-α	[119]
Isoliquiritigenin	*In vivo* (Wistar rats)	25 mg/kg (P. O for 20 d)	15 mg/kg (I. P. injection of a single dose)	3 w	↑Final body weights, ↓urea, ↑GFR, ↓Scr, ↑CrCl, ↑Salb, ↓urea, ↓Alb/Ucr ratio, ↓ROS/RNS, ↓MDA, ↑GSH, ↑SOD.	[127]
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 w	↑SOD, ↑CAT, ↓LPO	[136]

Flavanols

Flavanols, or flavan-3-ols, are a subclass of flavonoids, a class of plant compounds known for their antioxidant properties and potential health benefits. They are commonly found in foods such as fruits, vegetables, tea, and cocoa [115]. Flavanols, including epicatechin, catechin, epigallocatechin gallate, theaflavins, and procyanidins, are acknowledged for their antioxidant, anti-inflammatory, and potential anticancer properties and have been investigated for their renoprotective, cardioprotective, and hepatoprotective potential, highlighting their broader health benefits [116, 117]. Doxorubicin induces nephrotoxicity through oxidative stress, DNA damage, inflammation, and apoptosis in renal tissue [118]. Proanthocyanidin compounds are flavanols proven to reduce nephrotoxicity induced by doxorubicin in mice by reducing oxidative stress biomarkers such as MDA, increasing antioxidant enzymes such as SOD and GSH, and reducing markers of inflammation and apoptosis, including Cyclooxygenase-2 (COX-2), NO, and caspase-3 in kidney tissue [119].

Chalcones

Chalcones, a subclass of flavonoids with a C6-C3-C6 structure, act as crucial biogenetic precursors to diverse plant flavonoids and isoflavonoids [120]. Some examples of bioactive chalcone compounds known for their biological activities include phloretin, butein, isoliquiritigenin, licochalcone E, xanthohumol, and chalconaringenin [121, 122]. Chalcones are widely utilized for their diverse biological functions, including antioxidant, anti-inflammatory, neuroprotective [123], anticancer [124], hepatoprotective[125], and renoprotective [126]. Isoliquiritigenin, scientifically proven effective chalcones, improves kidney function by reducing urea and Urine Creatinine (Ucr) levels, increasing Glomerular Filtration Rate (GFR), improving Creatinine Clearance (CrCl), increasing Salb levels, and reducing ROS/RNS and MDA levels to protect against oxidative stress, while also increasing GSH and SOD activity [127].

Anthocyanins

Anthocyanins are water-soluble plant pigments belonging to the flavonoid group of compounds [128]. Delphinidin, petunidin, malvidin, cyanidin, peonidin, and pelargonidin are subclasses of anthocyanins found in diverse fruits and vegetables [129]. Additionally, these compounds contribute vivid red, purple, blue, and black tints to various plants [130]. They possess distinctive antioxidant properties, such as anti-inflammatory, anticancer, anti-apoptotic, renoprotective, hepatoprotective, and cardioprotective [131-135]. Administration of anthocyanins at doses of 75 mg/kg and 150 mg/kg has been proven to have a protective effect on the kidneys as a renoprotective agent in New Zealand rabbits experiencing oxidative stress due to doxorubicin induction, increasing SOD and CAT activity, and reducing LPO levels [136].

CONCLUSION

In summary, it can be concluded that doxorubicin induces nephrotoxicity through multiple pathways, including reduced antioxidant properties, impaired renal mitochondrial activity, and increased inflammatory reactions. Moreover, it is widely recognized that more research is needed to provide a comprehensive understanding of its fundamental mechanisms. Bioactive flavonoid compounds, namely quercetin, chrysin, rutin, kaempferol, morin, luteolin, apigenin, hesperidin, naringenin, diosmin, and anthocyanin, have been proven to have a significant impact in reducing kidney toxicity through various mechanisms involving the reduction of ROS, lipids peroxidation, mitochondrial permeability, and apoptosis. Investigating additional mechanisms of flavonoids in reducing doxorubicin-induced nephrotoxicity in the future is recommended.

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AUTHORS CONTRIBUTIONS

As the lead author, Dini Prastyo Wati spearheaded the project, designed the research framework, conducted the literature review, drafted the initial manuscript, and ensured its coherence. Syafruddin Ilyas, as the corresponding author, supervised the review process,

polished the content, ensured the manuscript's accuracy and proper English gmar, and managed the submission process and journal correspondence. All authors reviewed and approved the final manuscript, contributed to critical discussions, and provided valuable input to enhance the paper's quality.

CONFLICT OF INTERESTS

The authors state that they have no conflicting interests.

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