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Flavonoids as Modulators of Nrf2 Signaling Pathway in Alleviating Cisplatin-Induced Organ Toxicity

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Abstract

Cisplatin, a highly efficacious platinum-based anticancer agent, finds widespread application in the management of diverse malignant solid tumors, exhibiting commendable therapeutic outcomes. However, its clinical practice is limited due to its severe adverse effects, including nephrotoxicity, hepatotoxicity, cardiotoxicity, and ototoxicity. Although the exact mechanism of cisplatin toxicity is still unclear, oxidative stress, inflammation, mitochondrial damage, endoplasmic reticulum stress (ER stress), apoptosis, and DNA damage are involved in the processes of cisplatin toxicity. At present, a great amount of evidence has shown that flavonoids have beneficial effects on several cisplatin-induced organ toxicity by their powerful antioxidant properties. The activation of Nrf2 by flavonoids could potentially serve as a key mechanism for alleviating organ toxicity induced by cisplatin. In this review, we summarize the basic structure, regulation, and function of Nrf2, as well as focus on the role of Nrf2 in reducing cisplatin-induced nephrotoxicity, hepatotoxicity, and cardiotoxicity.

Keywords

Flavonoids, Cisplatin, Nrf2, Oxidative Stress, Natural Product

1. Introduction

Cisplatin, a kind of platinum drug, is widely used as a cancer chemotherapeutic agent for various solid tumors such as head and neck, bladder, breast, stomach, non-small cell lung, and ovarian cancers. Its fundamental anticancer mechanism is mainly attributed to activating DNA damage response in proliferating cancer

cells [1]. After cisplatin enters tumor cells, the chloride ions of cisplatin are replaced by water molecules, and the hydrates of cisplatin increase the affinity with DNA, resulting in DNA intra-strand and inter-strand crosslinks, consequent cell-cycle arrest, and cell death [2].

Unfortunately, cisplatin lacks action specificity and can cause DNA damage in normal cells, especially in cells that divide and proliferate quickly [3]. Besides, in order to prevent or confer cisplatin resistance, the strategy to increase the administered dosages of cisplatin is necessary, which further aggravates the adverse effects of cisplatin in normal cells and tissues [4]. Recently, increasing evidence has demonstrated cisplatin-related toxicities, including nephrotoxicity, hepatoxicity, ototoxicity, cardiotoxicity, intestinal toxicity, and neurotoxicity. In addition, it is becoming progressively evident that the excessive generation of reactive oxygen species (ROS), which in turn results in oxidative stress, plays a pivotal role in the development of organ toxicity induced by cisplatin [5]. Excessive ROS activated inflammatory cells such as monocytes, macrophages, and mast cells, which produced large amounts of cytokines and chemokines. Besides, the NF-κB and MAPK signaling pathways participate in the initiation of the canonical pathway of inflammation [6]. The accumulation of cellular ROS causes an increased level of misfolded proteins in the ER and activates unfolded protein response (UPR) [7]. Additionally, the elevation of mitochondrial ROS also activates the mitochondrial apoptosis pathway, which is manifested by the increase of Bax and the decrease of Bcl-2 [8]. To reverse those damages, many antioxidants, such as vitamins, have been widely studied to reduce cisplatin toxicity by inhibiting ROS, and certain effects have been achieved [9].

Flavonoids, which are found in a wide range of natural plants and berries, such as ginkgo hawthorn, blueberries, and grapes, have received considerable attention as a potential dietary supplement to reduce side effects of cisplatin [10]. Flavonoids are the most widespread polyphenolic compounds and are characterized by possessing a basic 15-carbon flavone skeleton (**Figure 1**), which consists of two aromatic rings (A and B rings) connected by a three-carbon bridge (C ring) [11]. Based on the different oxidative positions of A and C rings, flavonoids can be divided into the following six subclasses, including flavonols, flavones, flavanones, flavanols, isoflavones, and anthocyanidins [12]. The Nrf2 pathway, identified in the 1990s, is a key regulator of the cellular response to oxidative stress. Under normal conditions, Nrf2 is kept inactive in the cytoplasm by the protein Keap1. When ROS levels rise, Keap1 undergoes changes, allowing Nrf2 to translocate to the nucleus and activate antioxidant response element (ARE)-driven genes [13]. These genes enhance the cellular antioxidant defense and protect against oxidative damage.

Flavonoids, through the activation of the Nrf2 signaling pathway, have shown potential in enhancing cellular antioxidant defenses, thereby protecting against cisplatin-induced toxicity in organs such as the kidneys, liver, and heart. However, in tumor cells, dysregulated or excessive activation of Nrf2 may contribute to chemotherapy resistance by reducing ROS accumulation, thereby promoting tumor cell

survival. The dual role of Nrf2 in both normal and tumor cells underscores the need for targeted delivery strategies of flavonoids to optimize their therapeutic efficacy while minimizing potential adverse effects. This review will examine the critical role of the Nrf2 pathway in the oxidative stress response, explore the therapeutic potential of flavonoids in mitigating cisplatin-induced organ damage, and discuss targeted delivery strategies to enhance their efficacy while reducing the risk of cisplatin resistance and minimizing adverse effects.

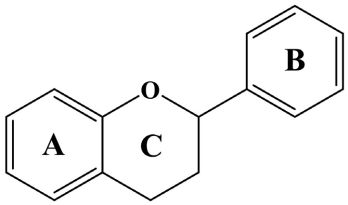

Figure 1. The basic structure of flavonoids.

2. The Structure and Function of Nrf2

Nrf2, a transcription factor, plays a key role in the protective effects of flavonoids by scavenging ROS and upregulating antioxidant genes [14]. As a member of the cap'n'collar (CNC) subfamily, Nrf2 has a bZIP structure with seven functional domains (Neh1-Neh7) (**Figure 2**) [15]. The Neh1 domain, responsible for DNA binding and dimerization with sMaf proteins, is critical for Nrf2 activation [16]. The Neh2 domain, containing the DLG and ETGE motifs, interacts with Keap1, a negative regulator of Nrf2, and facilitates its degradation via ubiquitylation. The Neh3 domain, along with Neh4 and Neh5, activates Nrf2 target genes. The Neh6 domain, rich in serine, forms a phosphodegron that GSK-3 can phosphorylate, leading to Nrf2 degradation via β-TrCP-mediated ubiquitination [17]. The Neh7 domain, which binds RXRα and other nuclear receptors like RARα, RARγ, and ERα, negatively regulates Nrf2 activity.

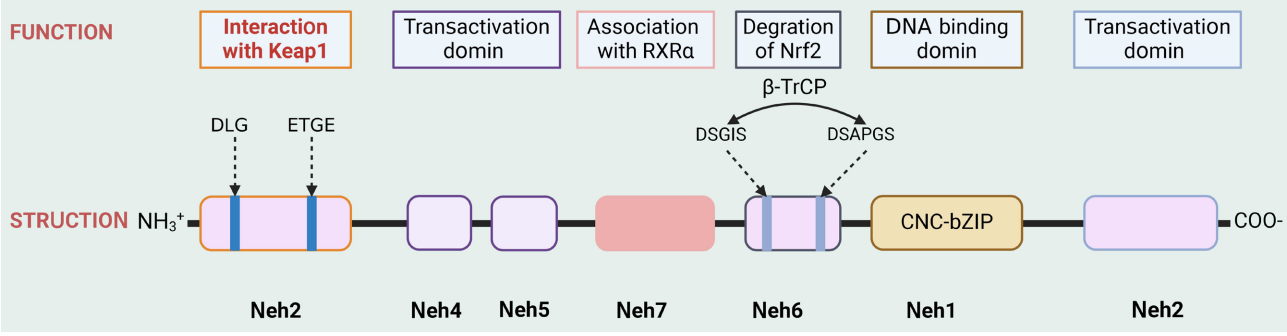

Figure 2. The basic structure and function of the Nrf2 protein.

3. The Regulation of Nrf2 Signaling Pathway

3.1. Keap1-Dependent Degradation (Canonical Pathway)

The cellular levels of Nrf2 are tightly regulated by Keap1, a redox-sensitive E3

ubiquitin ligase adaptor, through the "hinge and latch" model [18]. Under normal conditions, Keap1 binds to the Neh2 domain of Nrf2, leading to its recognition by Cul3 E3 ligase for continuous ubiquitylation and degradation [19]. Keap1 also contains a nuclear export sequence (NES) that mediates Nrf2 export from the nucleus to prevent accumulation [20]. Upon oxidative stress, reactive cysteine residues in Keap1 (C151, C273, C288) are oxidized, causing a conformational change that disrupts the Keap1-Nrf2 interaction [21]. Prolonged oxidative stress leads to Keap1 degradation via chaperone-mediated autophagy (CMA), increasing Nrf2 levels and initiating a positive feedback loop [22]. Nrf2 then translocates to the nucleus, binds to the antioxidant response element (ARE), and activates the expression of downstream genes such as HO-1, SOD-1, NQO-1, GPx, GCLC, and ferritin, which collectively maintain cellular redox balance [23].

3.2. Keap1-Independent Degradation (Non-Canonical Pathway)

3.2.1. p62 and p21 Can Regulate the Activation of Nrf2 Signaling Pathway

p62, or sequestosome1, is a selective autophagy receptor that targets intracellular substrates for degradation via the autophagy-lysosome pathway [24]. Kinases like mTOR, TAK, and AMPK can phosphorylate and activate p62 [25]. Phosphorylated p62 can interact with the Keap1-Nrf2 complex, competing with Nrf2 for Keap1 binding and promoting Keap1 degradation, likely via autophagy [26]-[28]. Additionally, phosphorylation of other proteins, such as the cell cycle regulator p21, has been shown to reduce the formation of Nrf2/Keap1 complexes [13].

3.2.2. PI3K/AKT Signaling Pathway also Can Regulate Nrf2

The PI3K/AKT signaling pathway plays a key role in regulating apoptosis by increasing anti-apoptotic proteins, allowing the elimination of dying cells and localized inflammation. Recent studies have shown that PI3K/AKT activation promotes Nrf2 expression by preventing its binding to Keap1, facilitating its translocation from the cytoplasm to the nucleus [29]. GSK-3, a downstream target of PI3K/AKT, is negatively regulated by this pathway through phosphorylation at Ser21 (GSK-3α) or Ser9 (GSK-3β) [30]. GSK-3 prevents Nrf2 from accumulating in the nucleus, which is essential for Nrf2's DNA binding [31]. Additionally, GSK-3 can phosphorylate Ser residues in the Neh6 domain of Nrf2, targeting it for ubiquitination via β-TrCP and the Cul3/Rbx complex [32]. GSK-3β also phosphorylates Fyn, leading to Nrf2 nuclear export and degradation [33]. However, during oxidative stress, PI3K/AKT activation inhibits GSK-3β, reducing Nrf2 degradation and promoting its stability [34].

3.2.3. MAKP Signaling Pathway Can Mediate the Activation of Nrf2

MAPKs, including p38 isoforms (α, β, γ, δ), ERKs, and JNKs, are crucial for translating extracellular signals into cellular responses, regulating gene expression, differentiation, and apoptosis [35]. Notably, p38 MAPK enhances the interaction between Keap1 and Nrf2, inhibiting Nrf2 activity [36]. Phosphorylated JNK antagonizes Nrf2's cytoprotective effects by directly interacting with the Neh1 domain,

leading to the downregulation of ARE-driven gene expression [37].

4. Nrf2: A Modulator in Inflammation and Apoptosis

4.1. Nrf2 Mediates the Inflammation via Modulating NF-κB Signaling Pathway

The Nrf2/HO-1 axis exerts anti-inflammatory effects. HO-1, an inducible enzyme, catalyzes the breakdown of heme into carbon monoxide and free iron and biliverdin into bilirubin, all of which have anti-inflammatory properties [38]. Evidence suggests that the Nrf2/HO-1 pathway negatively regulates the NF-κB signaling pathway through several mechanisms. First, Nrf2 activation reduces intracellular ROS levels, inhibiting ROS-mediated NF-κB activation [39]. Nrf2 also prevents the proteasomal degradation of IκB, thereby blocking the dissociation of the P65/P50 heterodimer and NF-κB activation [40]. Additionally, Nrf2 activation increases HO-1 levels, which enhances phase II enzyme expression, further blocking IκB degradation and promoting anti-inflammatory cytokine production to suppress NF-κB [41]. Furthermore, Nrf2 can inhibit inflammatory cytokine gene expression by binding to IL-6 and IL-1β, preventing RNA polymerase recruitment in macrophages [42].

4.2. Nrf2 Regulates the Apoptosis via Mediating ROS

Nrf2 plays a key role in regulating ROS, which can activate the three major apoptosis pathways: mitochondrial, extrinsic, and endoplasmic (**Figure 3**) [43].

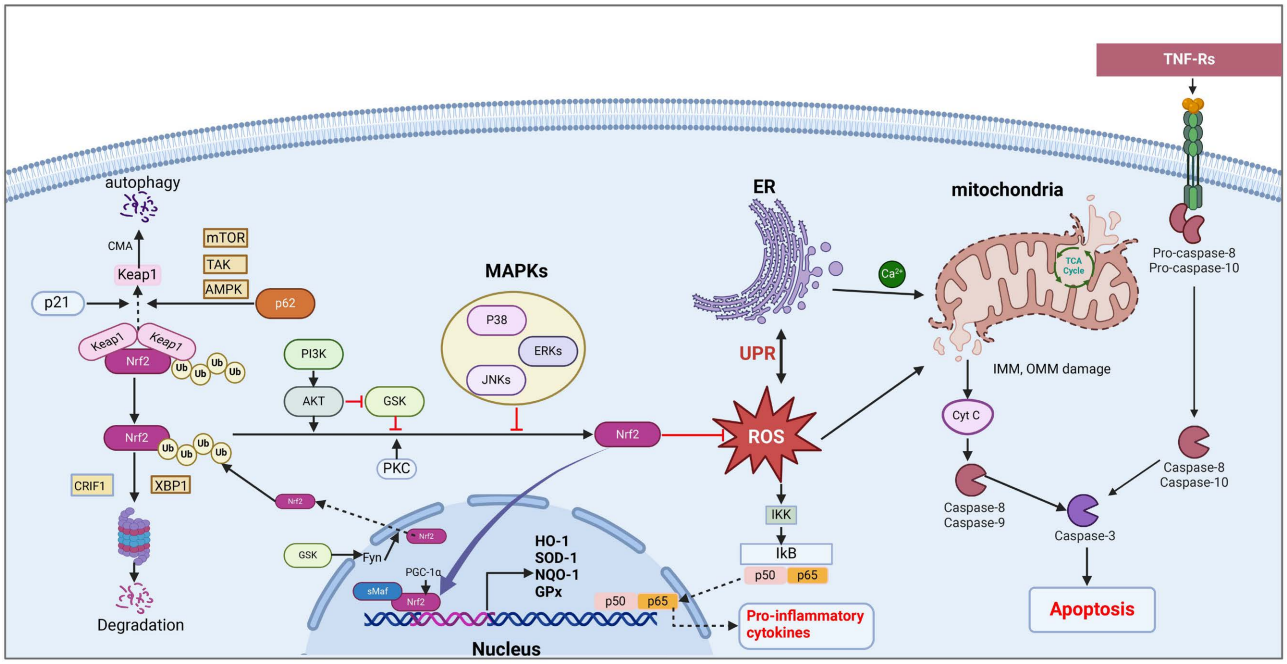

Figure 3. The regulation of Nrf2.

In the mitochondrial pathway, excessive ROS damages the mitochondrial inner

membrane, increasing its permeability and decreasing mitochondrial transmembrane potential [44]. This disrupts the outer mitochondrial membrane (OMM), leading to the release of cytochrome c (CytC), which activates caspases, particularly caspase-8 and caspase-9, ultimately activating caspase-3, the final executor of apoptosis [45] [46]. ROS also damages mitochondrial DNA (mtDNA), disrupts the respiratory chain, and reduces ATP synthesis [47]. ROS can activate tumor suppressor proteins like p53 and JNK, which further trigger pro-apoptotic Bcl-2 proteins (Bax, Bak), leading to mitochondrial outer membrane permeabilization [48]. In the extrinsic pathway, ROS initiate apoptosis by activating TNF-Rs, including TNF R1, Fas, DR3, TRAIL-R1, TRAIL-R2, and DR6 [48] [49]. In the endoplasmic pathway, ROS accumulation leads to oxidative protein modifications in the ER lumen, triggering endoplasmic reticulum stress. High levels of Ca^{2+} are released from the ER into mitochondria, opening the mitochondrial permeability transition pore (MPTP) and releasing ATP and CytC, which activates apoptosis [50].

5. Effects of Flavonoids on Cisplatin-Induced Organ Toxicity

5.1. Effects of Flavonoids on Cisplatin-Induced Nephrotoxicity

Cisplatin-induced nephrotoxicity

Cisplatin-induced nephrotoxicity, characterized by progressive decreases in glomerular filtration rate and increases in BUN and SCr, is a common side effect that significantly limits its clinical use. The risk of AKI in patients undergoing cisplatin-based chemotherapy ranges from 20% to 30% [51]. Moreover, patients who recover from AKI are at an elevated risk of developing chronic kidney disease [52]. Studies using rodent models have shown that a single high dose of cisplatin induces characteristic pathological changes of AKI, including vacuolation, protein cast formation, epithelial cell desquamation, and inflammatory cell infiltration in renal tubules [53].

Cisplatin-induced kidney injury involves several mechanisms, including DNA damage, mitochondrial dysfunction, ROS accumulation, ER stress, autophagy, inflammation, and apoptosis [54]. Emerging evidence shows that Nrf2-knockout mice experience more severe cisplatin-induced renal damage, histological changes, vascular permeability alterations, and inflammatory responses compared to wild-type mice [55]. ROS from cisplatin and reactive thiols from glutathione disrupt protein homeostasis in the ER, leading to the accumulation of unfolded/misfolded proteins, triggering the unfolded protein response (UPR), and resulting in ER stress-mediated apoptosis [56]. XBP1, a downstream chaperone of UPR, activates the Nrf2 pathway, reducing ER stress and apoptosis in rat kidneys [17] [57]. Additionally, ER stress exacerbates oxidative stress by releasing Ca^{2+}, which is taken up by mitochondria, leading to mitochondrial transition pore opening, CytC release, and mitochondrial apoptosis. In a cisplatin-induced acute injury model, phosphoglycerate mutase 5 inhibits Nrf2 nuclear translocation by forming a complex with Keap1 and Nrf2, promoting CytC release and aggravating kidney injury [58]. Nrf2 stimulates mitochondrial transcription factor A, enhancing the expression of

nuclear genes encoding mitochondrial electron transport chain subunits, thus boosting oxidative respiration [59]. Nrf2 also upregulates the ATP synthase α subunit, enhancing mitochondrial membrane potential ($\Delta\psi m$) [59]. Nrf2 depletion worsens cisplatin-induced renal tubular necrosis, fibrosis, ROS accumulation, and inflammation by inhibiting PINK1/Parkin-mediated mitochondrial autophagy [60]. Pro-inflammatory oxidative stress further activates NF-κB and induces cytokine overproduction, while disruption of the Nrf2/HO-1 anti-inflammatory axis exacerbates renal inflammation [61].

The protective effect of different flavonoids on cisplatin-induced nephrotoxicity

We explore the intricate molecular mechanisms by which flavonoids exert protective effects against cisplatin-induced nephrotoxicity, emphasizing their interactions with key cellular signaling pathways (**Figure 4**). Flavonoids modulate several critical pathways, including the Nrf2/Keap1, PI3K/AKT, MAPK, NF-κB, and mitochondrial pathways, to counteract oxidative stress, inflammation, and mitochondrial dysfunction in renal tissues (**Table 1**).

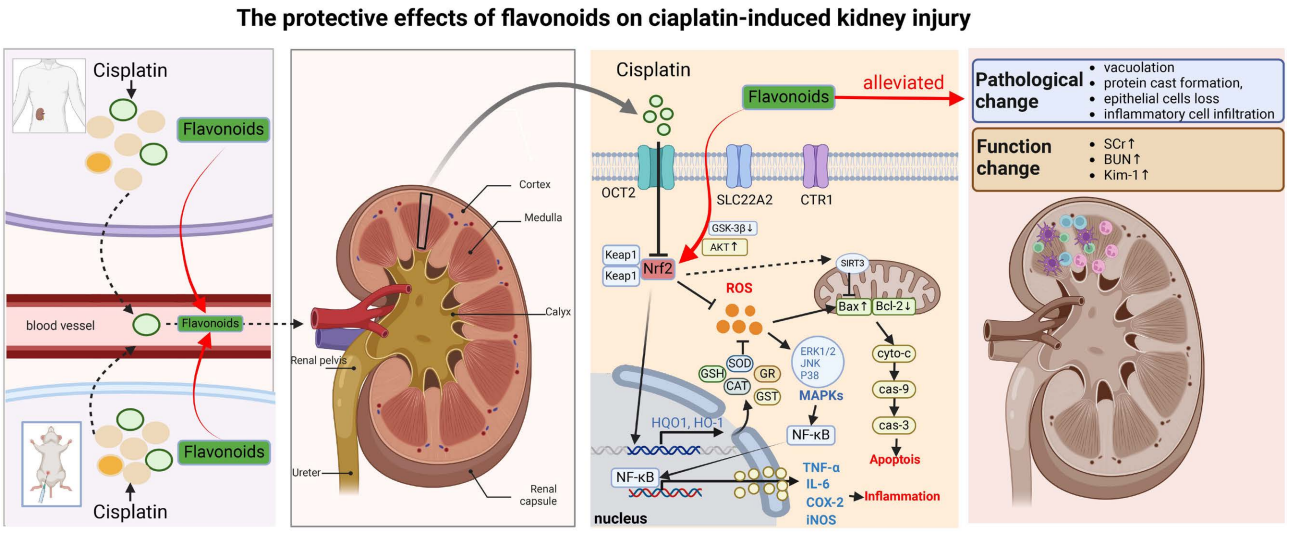

Figure 4. The protective effects of flavonoids on cisplatin-induced kidney injury.

Table 1. Protective effects of flavonoids on cisplatin-induced nephrotoxicity.

Flavonoids	Dosage	Cisplatin Dosage	Duration	Model	Results	Effects on Nrf2 Pathway	Reference
Taxifolin	25, 50 mg/kg	20 mg/kg	10 days	Swiss mice	↓BUN, SCr	↑Nrf2, HO-1 ↑GSH, SOD, CAT	[62]
H. salicornicum methanolic extract	100, 200, 400 mg/kg	7 mg/kg	15 days	Wistar rats	↓SCr, BUN ↓Kim-1	↓Keap1 ↑Nrf2, HO-1 ↑SOD, GSH, CAT	[63]
Liquiritigenin	15 mg/kg	20 mg/kg	3 days	BALB/c mice	↓BUN, SCr ↓apoptotic cells	↑GSK-3β inhibition ↑Nrf2/SIRT3 pathway	[65]
	25, 50 μM	20 μM	24 h	HK-2 cells	↑relative cell viability	↑Nrf2 nuclear levels	

Continued

Kaempferol	200 mg/kg	20 mg/kg	14 days	BALB/C mice	↓BUN, SCr	↑SOD, GST ↑Nrf2/HO-1 ↓iNOS ↓p53, Bax ↓NF-κB, TNF-α, IL-12 ↓p38, JNK, ERK1/2	[66]
Astilbin	50 mg/kg	8 mg/kg	10 days	C57BL/6 mice	↓BUN, SCr	↑SOD, CAT, GSH ↑Nrf2 ↓IL-6, IL-1β, TNF-α	[67]
	200 μM	100 μM	24 h	HER-293 cell line	↓apoptosis rate	↓ERK1/2, JNK, P38 ↑Nrf2, AKT ↓Bax, p53 caspase-3 ↓NF-κB, TNF-α, COX-2,	
Baicalein	50 mg/kg	20 mg/kg	15 days	BALB/C mice	↓BUN, SCr	↑GSH, SOD, CAT, NQO1 ↑Nrf2/HO-1 ↓MDA, iNOS ↓NF-κB, TNF-α, IL-6 ↓p38, JNK, ERK1/2	[68]
Galangin	25, 50, 100 mg/kg	8 mg/kg	11 days	Albino Wistar rats	↓BUN, SCr	↑GSH, SOD ↓MDA ↓TNF-α, IL-6 ↓Bax, caspase-3 ↑Bcl-2 ↓ERK1/2, JNK, P38 ↓NF-κB	[69]
Hesperetin	2.5, 5, 10 μM	20 μM	24 h	HK-2 cells	↓BUN, SCr	↑Nrf2, HO-1, NQO1 ↑SIRT6 ↓Bax, caspase-3	[70]
	50 mg/kg	20 mg/kg	12 h	Wistar rats	↓BUN, SCr	↑SOD, GSH ↑Nrf2, HO-1, NQO1 ↑SIRT6 ↓Nox4 ↓MAPKs ↓Bax, caspase-3	
Formononetin	75 mg/kg	12 mg/kg	5 days	Wistar rats	↓BUN, SCr ↓TNF-α	↑Nrf2, HO-1, NQO1 ↑CAT	[71]
	10, 25 μM	25 μM	48 h	HK-2 cells	↓apoptosis rate	↑Nrf2, HO-1, NQO1 ↑CAT	
Hyperin	20, 40. 80 mg/kg	20 mg/kg	7 days	C57BL/6 mice	↓BUN, SCr	↓MDA ↓TNF-α, IL-6, IL-1β ↓NF-κB ↑Nrf2/HO-1	[72]

1) Nrf2/Keap1 Pathway: Flavonoids like quercetin and taxifolin activate the Nrf2 pathway by disrupting its interaction with Keap1, leading to Nrf2's nuclear

translocation. In the nucleus, Nrf2 binds to the ARE to upregulate the transcription of genes such as HO-1 and NQO1, which neutralize ROS and enhance cellular repair mechanisms [62] [63].

2) PI3K/AKT Pathway: Apigenin activates PI3K/AKT, a key pathway in promoting cell survival [64]. By phosphorylating AKT, apigenin inhibits GSK-3β, preventing the degradation of Nrf2 and stabilizing its function, which enhances antioxidant responses. Liquiritigenin, a flavonoid derived from licorice, similarly stabilizes Nrf2 by inhibiting GSK-3β and activates Nrf2/SIRT3 to reduce mitochondrial damage, thus lowering ROS levels and improving renal function [65].

3) MAPK Pathway: Kaempferol and astibin inhibit MAPKs (ERK, JNK, and p38), which are central to the inflammatory response. By suppressing the activation of these kinases, these flavonoids reduce the production of pro-inflammatory cytokines such as TNF-α and IL-6, decreasing renal inflammation and improving cell viability in cisplatin-exposed renal cells [66] [67].

4) NF-κB Pathway: Baicalein and galangin suppress NF-κB signaling by inhibiting the phosphorylation of p65, a key subunit of the NF-κB complex. This inhibition reduces the transcription of pro-inflammatory cytokines, thereby mitigating inflammation and oxidative damage in renal tissues [68] [69].

5) Mitochondrial Protection: Flavonoids also confer mitochondrial protection against cisplatin-induced damage. Hesperetin activates SIRT6, a key regulator of mitochondrial function, which promotes mitochondrial integrity, reduces ROS production, and enhances mitochondrial bioenergetics, thereby mitigating mitochondrial dysfunction [70].

Studies by Hao *et al.* demonstrated that pretreatment with formononetin mitigated inflammatory changes and ROS accumulation in cisplatin-induced acute kidney injury (AKI), with Nrf2 activation as a likely target [71]. Similarly, Chao *et al.* found that hyperin administration in cisplatin-treated rats reduced oxidative stress markers such as MDA and pro-inflammatory cytokines (TNF-α, IL-6, IL-1β) through Nrf2 activation and NF-κB inhibition [72].

5.2. Effects of Flavonoids on Cisplatin-Induced Hepatotoxicity

Cisplatin-induced hepatotoxicity

Recent studies indicate that high-dose cisplatin treatment can result in acute drug-induced liver injury, limiting its clinical use [8]. Even low doses of cisplatin can accumulate in the liver, causing significant hepatic toxicity, which is evidenced by hepatic cord dissolution, hepatocyte vacuolization, and focal inflammatory lesions [73]. Elevated ALT and AST levels are commonly reported in patients receiving cisplatin, signaling liver cell destruction [74]. Additionally, serum LDH, a marker of cellular integrity, and serum ALP, an indicator of liver function, are significantly increased following cisplatin treatment [75]. In an *in vivo* study, Wistar mice injected with cisplatin showed marked increases in ALT and AST levels, along with hepatocellular degeneration and vacuolation observed under light microscopy [76].

Cisplatin-induced hepatotoxicity shares mechanisms with nephrotoxicity, primarily involving oxidative damage [77]. Cisplatin generates ROS in liver tissue, including hydroxyl radicals, hydrogen peroxide, and superoxide ions. The accumulation of these ROS impairs both nonenzymatic and enzymatic antioxidants, undermining the liver's natural antioxidant defenses and leading to lipid peroxidation [5]. Additionally, cisplatin-induced inhibition of Nrf2 reduces SOD and GSH levels, exacerbating oxidative stress in liver tissue [78]. This disruption of antioxidant systems also causes mitochondrial damage [79]. Cisplatin significantly alters respiratory chain activity in liver mitochondria, inhibiting NADH dehydrogenase (complex I) and succinate dehydrogenase (complex II), which depletes ATP [8]. Furthermore, cisplatin upregulates BAX and caspase-3 while downregulating Bcl-2, promoting the release of CytC and triggering liver cell apoptosis [80]. Nrf2 can mitigate this mitochondrial apoptotic pathway by reducing ROS accumulation. ROS accumulation triggers NF-κB translocation to the nucleus, where it activates inflammatory gene transcription, including TNF-α and iNOS [81]. NF-κB also inhibits Nrf2 activation by competing for CBP and recruiting HDAC3, exacerbating liver inflammation and oxidative damage caused by cisplatin [82].

The protective effects of flavonoids on cisplatin-induced hepatotoxicity

Flavonoids such as hesperidin, proanthocyanidin, morin hydrate, chrysin, and tangeretin exert potent hepatoprotective effects against cisplatin-induced liver toxicity primarily through the activation of the Nrf2 pathway (**Figure 5**) (**Table 2**).

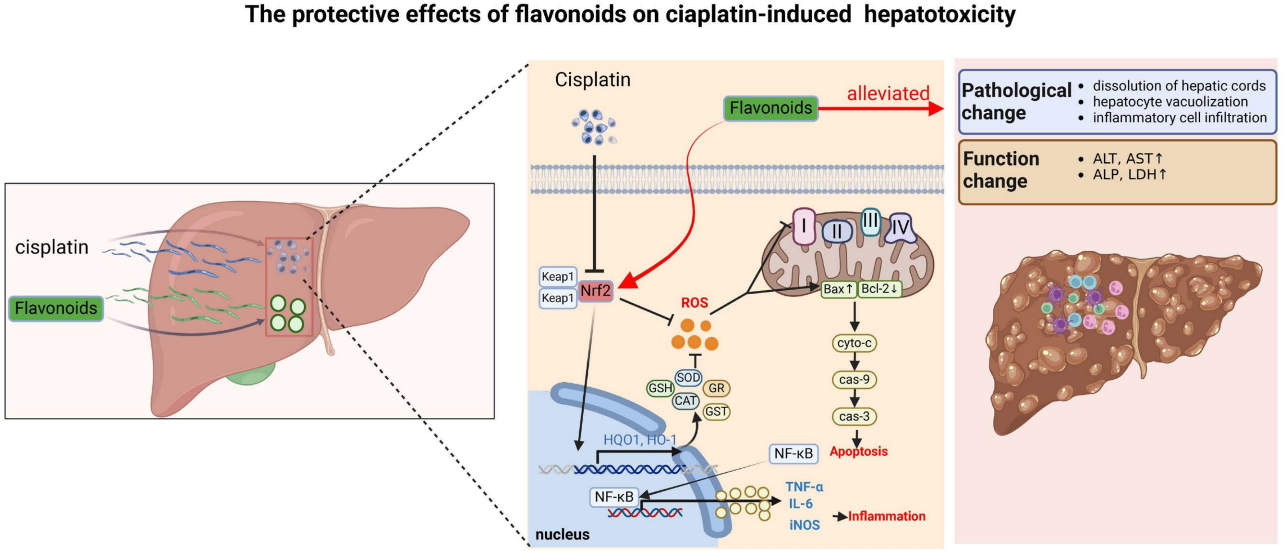

Figure 5. The protective effects of flavonoids on cisplatin-induced hepatotoxicity.

Hesperidin pretreatment significantly alleviates cisplatin-induced hepatotoxicity by modulating multiple signaling pathways, particularly by enhancing antioxidant defense systems and reducing inflammation [83]. It activates the PI3K/AKT-Nrf2-ARE signaling axis, which is crucial for upregulating the transcription of antioxidant

genes like HO-1 and NQO1 [29]. This activation helps neutralize ROS and attenuate oxidative stress. Additionally, hesperidin inhibits the NF-κB pathway, thereby suppressing the expression of pro-inflammatory cytokines such as TNF-α and IL-6 [84].

Table 2. Protective effects of flavonoids on cisplatin-induced hepatotoxicity.

Flavonoids	Dosage	Cisplatin Dosage	Duration	Model	Results	Effects on Nrf2 Pathway	Reference
Hesperidin	200 mg/kg	7.5 mg/kg	21 days	Albino rats	↓ALT, AST, ALP, Bilirubin	↑CAT, SOD, GSH ↓MDA, TNF-α ↓Bax, caspase-3	[83]
Hesperidin	100, 200 mg/kg	7.5 mg/kg	5 days	Wistar rats	↓ALT, AST	↑GSH, ↓NF-κB, ↑AKT	[84]
Proanthocyanidin	400 mg/kg	6 mg/kg	15 days	SD rats	↓ALT, AST, LDH, ALP	↑GSH, GPx, CAT ↓TNF-α, IL-6 ↓NF-kB, Bax, TLR-4	[85]
Morin Hydrate	50, 100 mg/kg	20 mg/kg	7 days	Swiss albino mice	↓ALT, AST	↑SOD, CAT, GSH ↓TNF-α, IL-6	[86]
Chrysin	25 mg/kg	7.5 mg/kg	14 days	Wistar rats	↓ALT, AST	↑SOD, CAT, GSH, GPx ↓TNF-α, NF-kB, COX2	[88]
Tangeretin	100 mg/kg	7.5 mg/kg	7 days	Wistar rats	↓ALT, AST ↓TC, TG	↑Nrf2, GPx, IL-10	[89]

Proanthocyanidin, a flavonoid from grape seeds, exerts hepatoprotective effects by both enhancing antioxidant activity and modulating inflammatory responses. In cisplatin-treated mice, proanthocyanidin activates the Nrf2/Keap1 pathway, promoting the expression of antioxidant enzymes like GSH, GPx, and CAT. This helps reduce ROS levels, contributing to the protective effects against oxidative damage [85]. Additionally, proanthocyanidin modulates the NF-κB signaling pathway, thus preventing inflammatory cascades and protecting liver function. This suggests that the Nrf2 and NF-κB pathways are key mediators of its hepatoprotective effects.

Morin hydrate provides protection against cisplatin-induced hepatotoxicity by reducing oxidative stress and inflammation [86]. It upregulates antioxidant enzymes like SOD, CAT, and GSH and simultaneously downregulates pro-inflammatory cytokines, including TNF-α and IL-6. These effects are likely mediated through the activation of the Nrf2/HO-1 pathway [87]. These findings underline the importance of Nrf2 in mitigating the oxidative and inflammatory damage associated with cisplatin.

Chrysin, known for its antioxidant and anti-inflammatory properties, has been shown to restore antioxidant enzyme levels like SOD and CAT in a cisplatin-induced liver injury model [88]. This protective effect is mediated through the activation of the Nrf2 pathway, which increases the expression of antioxidant enzymes. Furthermore, chrysin inhibits the NF-κB pathway, reducing the transcription of

inflammatory cytokines and thus mitigating inflammation and oxidative stress in liver tissues.

Tangeretin pretreatment enhances antioxidant defenses in cisplatin-treated liver tissues by restoring GSH and GPx levels. This is likely due to the activation of the Nrf2 pathway, which promotes the transcription of antioxidant genes. Additionally, tangeretin inhibits the MAPK signaling pathway, which is known for its involvement in inflammation and cell apoptosis. By reducing TNF-α levels and modulating key inflammatory mediators, tangeretin provides robust hepatoprotection by reducing both oxidative stress and inflammation in the liver [89].

5.3. Effects of Flavonoids on Cisplatin-Induced Cardiotoxicity

Cisplatin-induced cardiotoxicity

Cisplatin-induced cardiotoxicity affects 6% of patients and typically presents with abnormal ECG findings, including ST-T segment depression and first-degree atrioventricular block [90] [91]. As treatment progresses, cisplatin activates multiple signaling pathways such as PERK, MAPKs, PI3K/AKT, and NF-κB, promoting ROS accumulation, inflammatory cell infiltration, and apoptosome formation, leading to cardiomyocyte apoptosis [92]. Cardiac biomarkers like BNP, cTnT, CK-MB, and LDH are elevated, and left ventricular ejection fraction is decreased, indicating cardiotoxicity [93]. Histological changes such as misalignment of fibers, dark sarcoplasm, and nuclear alterations are also observed in models of cisplatin-induced cardiotoxicity [94].

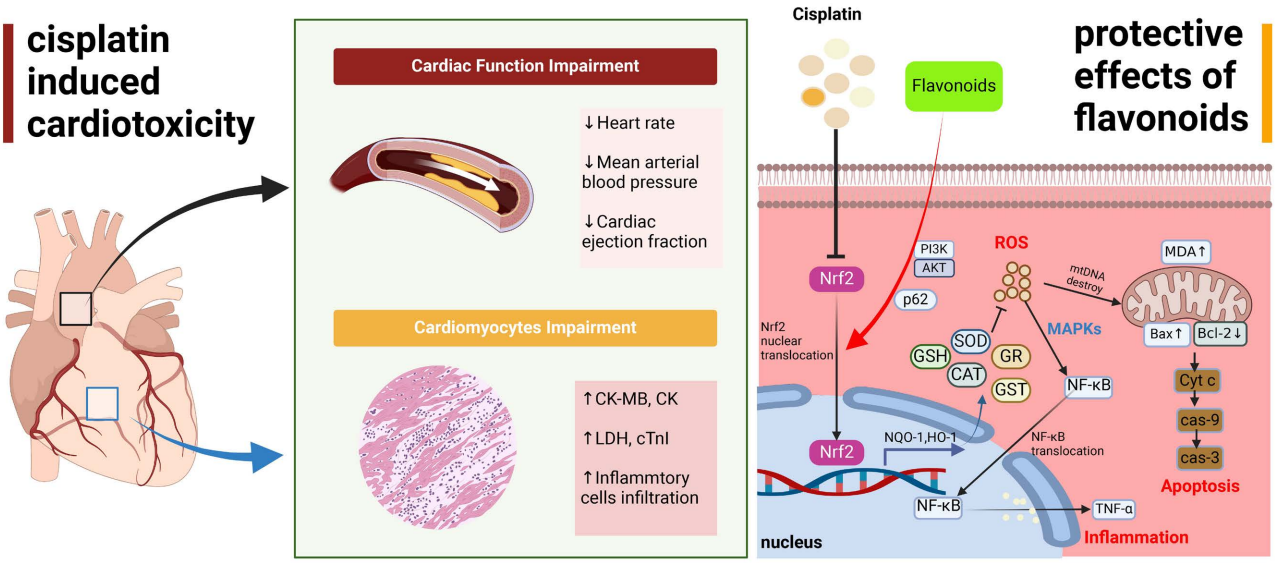

Figure 6. The protective effects of flavonoids on cisplatin-induced heart injury.

Emerging evidence suggests that activating the Nrf2/HO-1 pathway significantly mitigates cisplatin-induced heart injury. For instance, salvianolic acid B, a polyphenol compound, alleviates oxidative stress and cardiomyocyte apoptosis by upregulating Nrf2 expression [95]. In cisplatin-induced cardiotoxicity models,

low levels of PI3K and AKT are often observed, which may contribute to the toxicity. However, treatment with canagliflozin increases the expression of cardiac PI3K and AKT, promoting the dissociation of Keap1 from Nrf2 and enhancing its protective effects [92].

The protective effects of flavonoids on cisplatin-induced cardiotoxicity

Flavonoids may protect against cisplatin-induced cardiotoxicity primarily through the activation of the Nrf2 signaling pathway, leading to reduced ROS accumulation, enhanced antioxidant enzyme activity, and decreased inflammation and apoptosis (**Figure 6**) (**Table 3**).

Table 3. Protective effects of flavonoids on cisplatin-induced cardiotoxicity.

Flavonoids	Dosage	Cisplatin Dosage	Duration	Model	Results	Effects on Nrf2 Pathway	Reference
Silymarin	100 mg/kg	7.5 mg/kg	21 days	SD rats	↓CK, CK-MB, LDH, cTnI	↑SOD, CAT, GSH, GR, GST ↓H_2O_2, MDA	[96]
Silymarin	100 mg/kg	10 mg/kg	10 days	Albino rats	↓LDH, CK, ↓CK-MB ↓cTnI	↑SOD, GSH ↓MDA ↑mtDNA integrity	[97]
Hesperidin	100, 300 mg/kg	5 mg/kg	8 days	Kunming mice	↓cTnI, CK, LDH	↑SOD, CAT, GSH ↓MDA ↑p62, Nrf2	[99]
Hesperidin	50 mg/kg	7 mg/kg	14 days	SD rats	↓LDH, CK	↑SOD, GSH, CAT	[100]
Luteolin	20 mg/kg	3 mg/kg	21 days	C57BL/6 mice	↓CK-MB ↑EF, FS	↑SOD ↑Nrf2 ↑mRNA expression of NQO-1, HO-1	[103]
Icariin	15, 30 mg/kg	4 mg/kg	14 days	ICR mice	↓CK-MB, CK	↑SIRT1 ↓p38, caspase-3	[104]
	3, 6, 12 μM	40 μM	48 h	H9c2 cells	↓apoptosis rate	↑GSH-Px, CAT, SOD ↓MDA, NF-κB ↑mtDNA integrity ↓caspase-3, caspase-9 ↑PI3K/AKT	
Quercetin	5,10, 15, 20 μM	40 μM	36 h	H9c2 cells	↑Cell viability ↓LDH release	↑Nrf2, HO-1 ↓MAPK, NF-κB	[105]

Afsar *et al.* demonstrated that oral silymarin effectively mitigated oxidative stress, restored antioxidant enzyme activity, and reduced serum cardiac biomarkers following cisplatin administration [96]. Histological analyses confirmed these findings, showing improved myocardial architecture with reduced morphological changes, suggesting a protective role of silymarin against cisplatin-induced myocardial injury. The antioxidant properties of silymarin were linked to Nrf2 activation, as evidenced by increased expression of HO-1 and other antioxidant proteins [97]. Silibinin, a key component of silymarin, similarly activated the Nrf2/HO-1 pathway, alleviating ROS accumulation in an arsenic-induced cardiotoxicity model

[98]. Similarly, hesperidin treatment mitigated cisplatin-induced cardiotoxicity in rats by promoting the nuclear translocation of Nrf2, upregulating SOD, CAT, and other antioxidant enzymes. These effects resulted in reduced ROS accumulation, inflammation, and myocardial apoptosis, contributing to myocardial protection [99] [100]. The cardioprotective mechanisms of hesperidin are closely tied to its ability to activate the Nrf2 pathway, which enhances the cellular antioxidant defense system.

In an ischemia/reperfusion injury model, the cardioprotective effects of luteolin were compromised when AKT phosphorylation was inhibited by LY294002, a known PI3K/AKT antagonist, suggesting that luteolin mediates its protective effects via the PI3K/AKT signaling pathway [101]. AKT activation promotes Nrf2 nuclear translocation, further increasing the expression of antioxidant proteins like HO-1 and NQO-1 and thereby reversing oxidative damage and improving cardiac function [102]. In cisplatin-induced cardiotoxicity models, luteolin reduced CM-MB levels, improved cardiac function as indicated by enhanced ejection fraction and fractional shortening, and exhibited histopathological improvements, further suggesting its myocardial protective effects [103]. Additionally, luteolin inhibits Keap1 overexpression, promoting Nrf2 translocation and enhancing antioxidant defenses. Icariin, another flavonoid, exerts cardioprotective effects against cisplatin-induced cardiotoxicity by modulating both MAPK and PI3K/AKT signaling pathways. While the exact role of Nrf2 in icariin's cardioprotective effect remains to be fully elucidated, it is likely involved in modulating the antioxidant response and protecting myocardial cells from oxidative stress and inflammation [104].

Quercetin, a widely studied flavonoid found in various fruits, vegetables, and tea, protects H9c2 cardiomyocytes from cisplatin-induced cytotoxicity by activating the Nrf2 pathway, which upregulates the expression of key antioxidant enzymes. Additionally, quercetin inhibits the MAPK/NF-κB/IL-8 signaling pathway, reducing inflammatory cytokine production and further protecting myocardial cells from cisplatin-induced damage [105].

6. Dual Role of Nrf2 in Normal and Cancer Cells: Implications for Cisplatin Resistance and Clinical Use of Flavonoids

The Nrf2 pathway is essential for cellular defense against oxidative stress and damage, and flavonoids, as potent activators of Nrf2, can significantly modulate this pathway. However, the effects of Nrf2 activation differ dramatically between normal and cancer cells [4], especially in the context of cisplatin treatment. This divergence raises important considerations for the clinical use of flavonoids as adjunct therapies to alleviate cisplatin-induced organ toxicity, particularly in cancer patients.

6.1. Nrf2 Activation in Normal Cells: Protective Effects

In normal cells, Nrf2 activation provides a robust defense against oxidative damage

by inducing the expression of antioxidant genes such as HO-1, NQO1, and various phase II detoxifying enzymes [14]. In the context of cisplatin treatment, which induces oxidative stress and cellular injury, flavonoids such as quercetin, hesperidin, and luteolin activate Nrf2, enhancing the antioxidant response and protecting tissues like the liver, kidneys, and heart from cisplatin-induced damage [70] [103] [105]. This protective effect is crucial for maintaining the integrity of normal tissues during chemotherapy, reducing organ toxicity, and improving patient outcomes.

6.2. Nrf2 Activation in Cancer Cells: A Double-Edged Sword

In contrast, cancer cells often exhibit aberrant or sustained activation of Nrf2 [106]. While this pathway helps protect tumor cells from the cytotoxic effects of cisplatin and contributes to the phenomenon of cisplatin resistance [107]. By enhancing the expression of detoxifying enzymes and increasing antioxidant defenses, Nrf2 reduces the intracellular concentration of reactive cisplatin metabolites, thus preventing cell death and enabling the survival of malignant cells [108]. Some studies even suggest that Nrf2 may function as an oncogene and that inhibiting Nrf2 expression could improve chemoresistance [109] [110].

Flavonoids, by activating Nrf2, may inadvertently exacerbate this issue, particularly when used as adjuncts to cisplatin treatment. This paradox highlights the need for careful consideration of the timing, dosage, and context in which flavonoids are administered to avoid promoting resistance in cancer cells while still providing protection to normal tissues.

6.3. Mitigating the Risk of Cisplatin Resistance: Targeted Delivery Strategies

To harness the protective benefits of flavonoids while minimizing the risk of Nrf2-mediated cisplatin resistance in cancer cells, targeted delivery systems can be employed. These strategies aim to localize the flavonoid's effects to normal tissues, where their antioxidant and cytoprotective properties can alleviate cisplatin-induced toxicity without activating Nrf2 in tumor cells, where it could promote resistance.

Nanoparticle-Based Drug Delivery: Flavonoids and their nanoparticle formulations have shown significant potential in both anticancer activity and alleviating side effects [111]. Curcumin nanoparticles have been shown to reduce cisplatin-induced hepatotoxicity and nephrotoxicity by inhibiting ROS generation [112]. Similarly, curcumin and quercetin lipid microsphere nanoparticles activate Nrf2 to suppress ROS and inflammation, ultimately mitigating cisplatin-induced nephrotoxicity [113]. Quercetin phosphate nanoparticles enhance the tumor microenvironment by inhibiting Wnt16 expression in fibroblasts, thus improving the antitumor efficacy of cisplatin [114]. However, there is currently a lack of studies comparing the Nrf2 expression changes in both tumor and normal cells after the delivery of flavonoid nanoparticle formulations.

Controlled Release Systems: Controlled-release formulations of flavonoids, which gradually release the active compound over time, have demonstrated both anti-cancer and anti-inflammatory effects [115]. Multilayer nanoparticles co-encapsulating luteolin and cisplatin exhibit controlled release and prolonged drug availability, enhancing antitumor efficacy while minimizing toxicity [116]. These systems represent a promising approach to improve the therapeutic index of flavonoids in combination with cisplatin.

7. Conclusion and Future Perspective

The onset of cisplatin-induced organ toxicity is accompanied by ROS accumulation, ER stress, mitochondrial damage, inflammatory response, and apoptosis. The benefits of flavonoids against cisplatin-induced organ toxicity are associated with the activation of Nrf2, which elevates the expression of HO-1, SOD-1, NQO-1, and other oxidant genes to reduce ROS accumulation, ER stress, inflammatory response, and apoptosis. In addition, flavonoids may regulate the Nrf2 signaling pathway by phosphorylating and activating some proteins, such as p62 and p21, and activating PI3K/AKT and MAPK signaling pathways.

Although this article summarizes a great number of studies on the reduction of cisplatin toxicity by activating Nrf2 by flavonoids, these studies mainly focus on the preclinical stage. While some clinical trials suggest that flavonoids can alleviate chemotherapy side effects and enhance antitumor activity, these studies are primarily limited to Phase I trials and lack a comprehensive exploration of the underlying mechanisms of action. Therefore, more extensive clinical studies are necessary to investigate the protective effects of flavonoids further and clarify the mechanisms by which they exert their benefits [117] [118]. In addition, several preclinical studies showed the activation of Nrf2-induced cancer cell resistance to cisplatin because of the mechanism of cisplatin-induced cancer cell death via enhancing ROS accumulation [4]. Due to the contradicting roles of Nrf2 in normal and tumor cells, more preclinical and clinical evidence are needed to explore the protective effects of flavonoids against cisplatin-induced organ toxicity by activating Nrf2 and the potential to increase the possibility of resistance to cisplatin.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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