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**Review**

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OXFORD

# Natural product mitigation of ferroptosis in platinum-based chemotherapy toxicity: targeting the underpinning oxidative signaling pathways

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## Abstract

**Objectives:** Platinum-based anticancer chemotherapy (PAC) represents a cornerstone in cancer treatment, retaining its status as the gold standard therapy. However, PAC's efficacy is countered by significant toxicities, such as nephrotoxicity, ototoxicity, and neurotoxicity. Recent studies have linked these toxicities to ferroptosis, characterized by iron accumulation, reactive oxygen species generation, and lipid peroxidation. This review explores the mechanisms underlying PAC-induced toxicities, focusing on the involvement of ferroptosis with three major PAC drugs—cisplatin, carboplatin, and oxaliplatin. Further, we provide a comprehensive analysis of the natural product mitigation of PAC-induced ferroptotic toxicity.

**Key findings:** The mechanistic role of ferroptosis in cisplatin- and oxaliplatin-induced toxicities has been investigated, while studies on carboplatin-induced ferroptotic toxicities are lacking. Natural compounds targeting molecular pathways of ferroptosis have been explored to mitigate PAC-induced ferroptotic toxicity.

**Conclusion:** While ferroptosis in cisplatin- and oxaliplatin-induced toxicities has been investigated, there remains a notable dearth of studies examining its involvement in carboplatin-induced toxicities. Hence, further exploration is warranted to define the role of ferroptosis in carboplatin-induced toxicities, and its further mitigation. Moreover, in-depth mechanistic evaluation is necessary to establish natural products evaluated against PAC-induced ferroptosis, as PAC adjuvants.

**Keywords:** platinum-based anticancer drugs; cisplatin toxicity; ferroptosis; natural ferroptosis inhibitors

## Introduction

Despite decades of research, cancer remains a debilitating disorder with almost 10 million deaths in 2020 [1]. Projections indicate a continuous rise in cancer incidence in the future. A 2022 study in India predicted a 12.8% increase in cancer cases by 2025 compared with 2020 [2]. While significant progress has been made in pharmacological interventions, including diagnostic marker screening and the adoption of multimodal therapies, aggressive forms of cancer continue to persist. Molecular therapies targeting specific mutations are being explored, yet chemotherapy remains the primary treatment option for many aggressive tumors [3], with platinum-based anticancer chemotherapy (PAC) being a common choice [4].

PAC, which includes cisplatin, carboplatin, and oxaliplatin, is pivotal in treating solid tumors. Cisplatin was discovered by chance, during an investigation into the effect of electricity on an *Escherichia coli* culture using platinum electrodes in 1965. It was reported that passing current across the electrode set-up inhibited the division of the *E. coli* culture and promoted filamentous growth, which was eventually identified to have been the effect of cisplatin [5]. The potential of cisplatin as an anticancer agent was recognized in the year 1970, and its use as a chemotherapeutic agent was approved by the FDA in 1978 [6]. However, concerns over cisplatin toxicity spurred the development of carboplatin, a second-generation drug with reduced toxicity but cross-resistance with cisplatin due to a similar mechanism of action [7, 8]. Subsequently, oxaliplatin, a third-generation drug, was developed to address this issue while maintaining efficacy similar to cisplatin [9].

While platinum-based drugs are highly effective, extensive modifications have been made to lower their toxicity. In spite of the efforts, they are still known to cause deleterious impacts on the health of cancer patients in the form of nephrotoxicity, neurotoxicity, testicular toxicity, ototoxicity, hepatotoxicity, ovarian toxicity, and pulmonary toxicity [10–15]. Due to these debilitating side effects and susceptibility to developing

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chemoresistance, platinum-based drugs remain a concern for clinicians and patients till date [16, 17]. Numerous studies have demonstrated that PAC-induced toxicities in healthy tissues are mediated through diverse mechanisms such as oxidative stress, inflammation, endoplasmic reticulum (ER) stress, caspase-dependent apoptosis, and other signaling disruptions. Additionally, emerging research suggests that ferroptosis, a nonapoptotic form of regulated cell death dependent on iron, also plays a novel role in PAC-induced toxicity. Ferroptosis is characterized by excessive iron accumulation, that leads to a subsequent increase in reactive oxygen species (ROS) levels and lipid peroxidation. This further culminates into oxidative damage to the mitochondria and other cellular components, causing cell death [18–20]. This review explores the toxicity mechanisms of PAC, and the associated mechanistic involvement of ferroptosis in mediating the damage. Furthermore, while natural products have shown potential to combat PAC-induced toxicities without hampering their anticancer efficacy [16, 21], few studies have investigated their potential to inhibit ferroptosis. Hence, this review also aims to elucidate the potential of various natural products as adjuvants against ferroptosis in PAC-induced organ toxicity.

## Anticancer mechanism of PAC drugs

Anti-cancer drugs function through various mechanisms, such as apoptosis induction, anti-proliferative effects, inhibition of protein synthesis, inhibition of DNA replication, cell cycle arrest, and so on [22]. PAC drugs such as cisplatin primarily inhibit DNA replication, leading to DNA damage, cell cycle arrest, apoptosis, and eventual cell death [23–25]. Cisplatin (Fig. 1A), a platinum complex linked to two amino and two chloro-ligands in a *cis* configuration (*cis*-[$PtCl_2(NH_3)_2$]), enters the intracellular environment either via a passive diffusion mechanism, or with the active facilitation of membrane-bound proteins such as the copper transporter-1 channel [25]. Upon entering the cell, cisplatin undergoes a process called hydration, where one chloro-ligand is replaced by a water molecule yielding a positively charged, mono-aquated form of cisplatin ($[PtCl(OH_2)(NH_3)_2]^+$). This mono-aquated form of cisplatin enters the nucleus and attacks the 7th nitrogen molecule (N7) of guanine, giving rise to a monofunctional adduct. This adduct is neutral in nature, following which the second chloro-ligand is hydrolyzed. The platinum ion then covalently links to another nucleophilic center of a nucleobase such as guanine or cytosine, either on the same strand, forming an intra-strand crosslink, or on the opposite strand, forming an inter-strand crosslink [8, 25, 26]. The formation of crosslinks throughout DNA prevents the binding of DNA and RNA polymerase, due to which the replication and transcription of DNA are inhibited, respectively. Additionally, this prevents the expression of the *MDM2* gene, leading to p53 activation, promoting the expression of the pro-apoptotic factor BAX, which enters the mitochondria and releases cytochrome c to activate the caspase pathway for the eventual degradation of cellular content [26]. Carboplatin (Fig.1B), with bidentate cyclobutene ligand, forms the same crosslinked adducts as that of cisplatin, but exhibits greater stability in the intracellular environment, due to which the hydration rate and duration of action are prolonged, accompanied by lowered side effects [27]. Finally, oxaliplatin (Fig. 1C) containing a diamino cyclohexane ligand, mainly forms intra and inter-strand adducts between guanine and adenine, similar to that of cisplatin [28].

## Side effects and toxicity mechanisms of PAC drugs

Extensive studies have emphasized the role of PAC drugs in inducing toxicity in various organs such as the kidneys, liver, testis, heart, and brain, resulting in significant side effects such as nephrotoxicity, hepatotoxicity, testiculotoxicity, cardiotoxicity, and peripheral neuropathy, respectively [10, 13]. While the precise mechanisms of these toxic side effects remain incompletely understood, there are established intracellular signaling pathways implicated in driving the adverse effects (Fig. 2).

### Oxidative stress and Keap1/Nrf2/ARE/HO-1 signaling

Numerous studies have indicated the role of platinum-based drugs in triggering oxidative stress in nontarget tissues. Masuda *et al.* demonstrated the production of ROS by cisplatin in a cell-free system, with the observed generation of hydroxyl ($OH^-$) radical and superoxide anion ($O_2^-$) upon the formation of intra- and inter-strand crosslinks with DNA [29]. An investigation performed by Podratz *et al.* demonstrated that cisplatin apart from targeting the nuclear DNA and generating ROS, also causes mitochondrial DNA damage, as shown through the inhibition of mtDNA replication and transcription by cisplatin in dorsal root ganglion neurons, leading to oxidative stress [30]. Similarly, Lomeli *et al.*observed cisplatin-induced mitochondrial ROS generation in the hippocampal neurons of rats causing cognitive defects, and further reported that cisplatin promotes ROS production in both mitochondria by damaging mitochondrial DNA, and

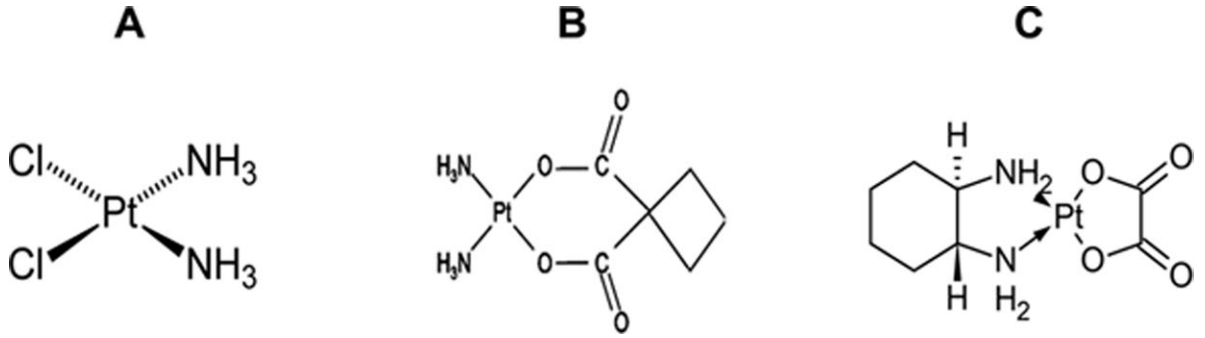



**Fig. 1.** Chemical structures of (A) cisplatin, (B) carboplatin, and (C) oxaliplatin.

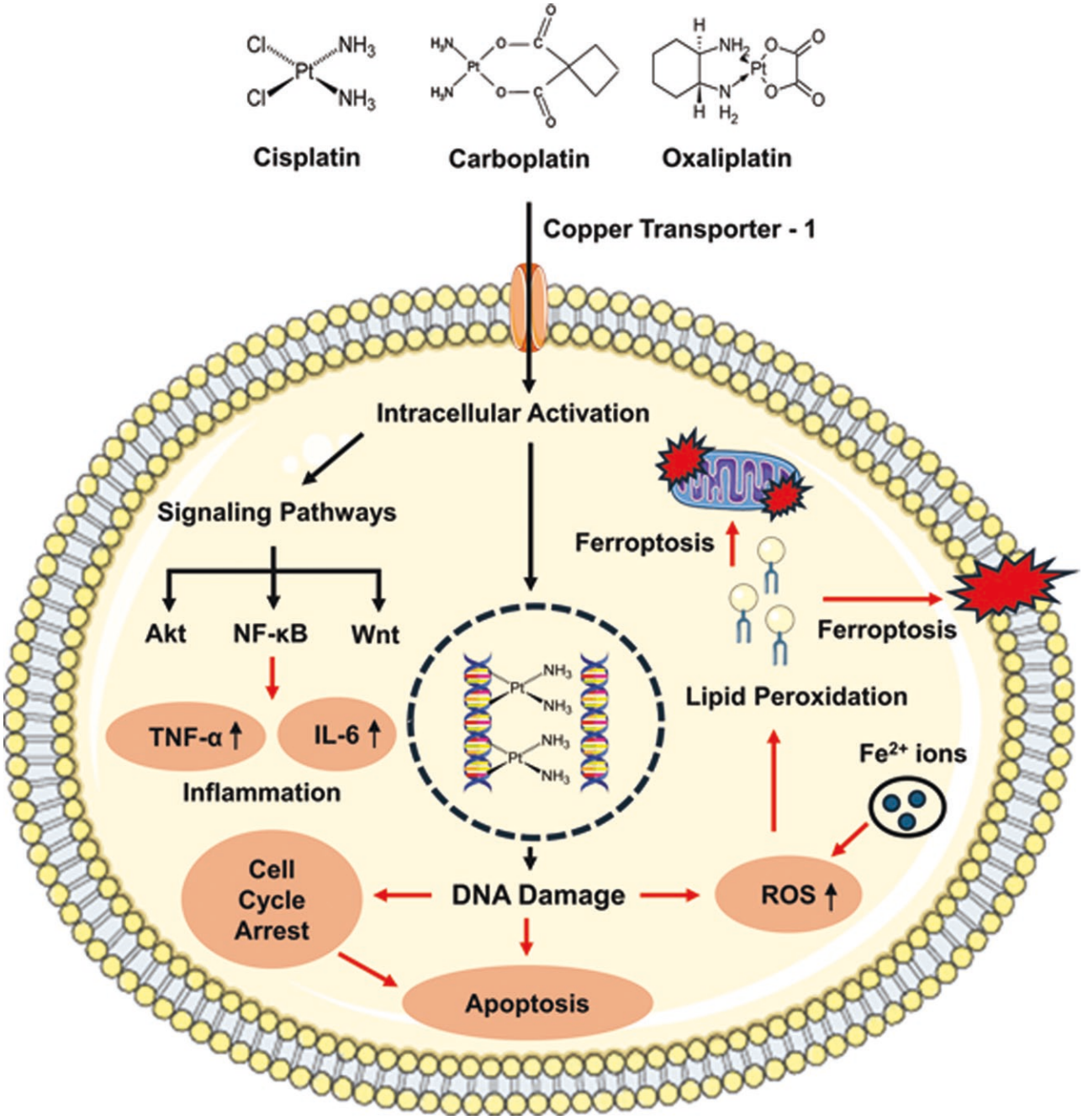



**Fig. 2.** Representation of molecular mechanisms of PAC-induced toxicity.

in the nucleus by damaging nuclear DNA, leading to elevated oxidative stress [31]. Wells *et al*. observed that cisplatin inhibited the thioltransferase enzyme, an antioxidant enzyme responsible for catalyzing the reduction of dehydroascorbate to ascorbate through a reduced glutathione-dependent mechanism, which further disrupted the antioxidant system and exacerbated oxidative damage in nontargeted tissues [32]. This spurred further investigation into cisplatin's potential impact on other cellular antioxidants elements. Oxidative stress in cells can be assessed by measuring lipid peroxide and reduced GSH levels, as well as the expression levels of enzymes such as superoxide dismutase (SOD) and glutathione peroxidase-4 (GPX-4), which form a crucial part of the antioxidant system of a cell [33]. A study by Babu *et al*. reported increased levels of lipid peroxides in cisplatin-treated mice, along with reduced GSH levels and altered enzymatic activity of catalase (CAT), SOD, and GPX-4. These effects were significantly attenuated through the administration of glutathione esters [34].

Additionally, carboplatin and oxaliplatin have also been reported to induce oxidative stress. Cheng *et al*. reported that mice treated with carboplatin showed abnormalities in cardiac histology, which was accompanied with elevated ROS levels and apoptotic markers, indicating that carboplatin induced oxidative stress in the cardiac region [35]. Further, these effects were attenuated through the administration of ROS scavengers, pravastatin and N-acetylcysteine (NAC) [35]. Similarly, a study by Husain *et al*. showed

that carboplatin treatment increased oxidative stress in rat cochlea, contributing to ototoxicity [36]. Tabassum *et al.* [37] demonstrated oxaliplatin-induced oxidative stress in the liver mitochondria of rats, leading to elevated lipid peroxide levels and decreased GSH levels [37].

Wang *et al.* [38] reported that cisplatin lowered the antioxidant enzyme activity of SOD, CAT, and glutathione peroxidase, while malondialdehyde (MDA) levels increased within mice testes, indicating the induction of reproductive toxicity [38]. Similarly, studies have also demonstrated the potential of PAC drugs in inducing oxidative stress [16, 18, 39, 40] in other target organs of animal models.

During oxidative stress, Keap1 undergoes phosphorylation at its serine residues, marking it for proteasomal degradation. This allows Nrf2 to translocate to the nucleus, where it upregulates the expression of various target genes, including antioxidant response elements (AREs) and antioxidant enzymes such as HO-1 (heme-oxygenase-1), which are critical regulators of oxidative stress [41]. In response to oxidative stress induced by PAC drugs, the Keap1/Nrf2/ARE/HO-1 signaling pathway is activated within cancer cells, providing a protective antioxidant effect that can lead to chemoresistance [42]. However, in nontarget tissues, PAC drugs exhibit a unique relationship with this signaling pathway. Cisplatin-induced ROS has been found to inhibit the nuclear translocation of Nrf2, thereby suppressing the activation of antioxidant genes, and/or Nrf2/ARE/HO-1 signaling pathway, ultimately contributing to PAC toxicity. For example, cisplatin deactivates the Nrf2/HO-1 and SIRT1/PPARγ/Nrf2/HO-1 (SIRT1—Sirtuin 1; PPARγ – Peroxisome proliferator-activated receptor gamma) signaling pathways, to aggravate oxidative stress in models of cisplatin-induced pulmonary toxicity [43], nephrotoxicity [44], and testicular toxicity [45].

## Inflammation-linked signaling pathways

Nephrotoxicity is one of the major side effects that has been linked to PAC toxicity, particularly induced by cisplatin [46]. Cisplatin-induced acute kidney injury often progresses to chronic kidney diseases [47, 48]. PAC drugs reach the kidney for excretion, but due to their rapid hydration rate, toxic effects are induced in the nephrons. This damage is manifested in the form of oxidative damage and inflammation [49]. Inflammation is the second most associated toxic effect of PAC drug administration. The nuclear factor-kappa B (NF-κB) plays a key role in PAC-induced inflammation and tissue damage [50, 51]. Normally suppressed in the cytosol by IκB proteins, NF-κB becomes activated under a condition of stress or infection, translocating to the nucleus to initiate signaling by pro-inflammatory cytokines such as TNF- α, IL-6, etc [45, 52]. Studies have reported that cisplatin possesses the potential to induce NF-κB signaling, which results in inflammation-induced nephrotoxicity [53]. Cisplatin administration shows elevated levels of renal inflammatory markers such as TNF- α, IL-6, NF-κB p65, and its phosphorylated forms, leading to the enhancement of the nuclear activation and transcription of target genes specific for inflammatory cascades, triggering organ damage [53, 54]. Similarly, studies have reported that mice treated with oxaliplatin show an upregulation of NF-κB, TNF-α, and IL-6, in the L4-L5 dorsal root ganglia, leading to nerve damage and neuropathy [55].

With the established role of NF-κB activation in mediating PAC toxicity, understanding the mechanisms by which PAC drugs induce NF-κB activation is crucial. One of the main signaling pathways implicated in NF-κB-mediated PAC toxicity is the JAK/STAT-3 pathway (JAK—Janus kinase; STAT—Signal transducers and activators of transcription) [56, 57]. JAK/STAT-3 signaling activates NF-κB inflammatory damage in PAC toxicity, where the phosphorylation and activation of JAK promote the translocation of STAT-3 into the nucleus. Subsequently, STAT-3 triggers the expression of pro-inflammatory cytokines such as TNF- α that are commonly implicated in NF- κB signaling [56, 57]. In addition to NF-κB signaling, other studies suggest the role of the toll-like receptor 4 (TLR4), nod-like receptor protein 3 (NLRP3), and the mitogen-activated protein kinases/extracellular signal-regulated kinases (MAPK/ERK) pathways, in PAC-induced inflammatory damage [58, 59]. TLR4 promotes cisplatin toxicity by activating NF-κB p65, interferon regulatory factor 3 (IRF3), extracellular signal-regulated kinases 1/2 (ERK1/2), and p38 mitogen-activated protein kinases (p38MAPKs) [50, 57]. Cisplatin-mediated ROS and subsequent NF-κB activation further trigger the assembly of the NLRP3 inflammasome, as demonstrated by Li *et al.* [60]. The study also confirms that the inhibition of the NLRP3 inflammasome attenuates renal fibrosis induced by cisplatin. In corroboration, the TLR4/NF-κB/NLRP3 signaling pathway has been shown to be involved in promoting inflammatory processes, leading to cisplatin-induced nephrotoxicity [59].

Moreover, oxaliplatin has been reported to activate the expression of MAPK and ERK proteins in neuropathic pain [61]. In a rat model of oxaliplatin-induced peripheral neuropathy, upregulation of NF-κB, JNK, p38 MAPK, ERK1/2, and TNF-α gene expression was observed, compared with the control rats [62]. Apart from oxaliplatin-induced neuropathy, Azouz *et al.* [44] and Potočnjak *et al.* [56] reported the upregulation of MAPK/NF-κB and NF-κB/STAT-3/ERK1/p-FOXO3a signaling pathways, respectively, in the case of cisplatin-induced nephrotoxicity. However, increased expression of STAT-3 has also been associated with protection against cisplatin-induced ototoxicity [63].

The large base of findings clearly demonstrates that a broad network of signaling pathways is altered, contributing to the inflammatory mechanisms associated with PAC toxicity and organ damage. Moreover, the involvement of immunomodulation has been explored. PAC drugs may trigger excessive immune responses at nontarget sites, thereby promoting inflammation and damage [64]. For instance, the study by Wafai *et al.* showed that oxaliplatin administration in rats caused an alteration in the morphology of enteric neurons, and increased the levels of nitric oxide synthase immunoreactive neurons, which can be linked to neuropathy and colonic dysfunction [65]. Similarly, Vera *et al.* [66] demonstrated severe enteric neural damage in rats provided with multiple cisplatin injections, with a marked increase in nitric oxide synthase immunoreactive neurons.

## Apoptosis, endoplasmic reticulum stress, and autophagy

The toxicity of PAC drugs is mediated through the dysfunction of multiple signaling pathways [7]. Mounting evidence suggests that the dysregulated molecular pathways triggered by PAC drugs ultimately lead to cell cycle arrest, followed by

apoptosis induction. PAC drugs such as cisplatin accumulate in healthy tissues and undergo metabolic transformations to produce toxic metabolites. These metabolites disrupt DNA integrity, antioxidant balance, and mitochondrial function, leading to oxidative stress, inflammation activation, and apoptotic responses. This is known as the extrinsic pathway of apoptosis [44]. However, studies by Lee *et al*. [67] and Park *et al*. [68] have indicated that apoptosis in distal renal epithelial cells in cisplatin nephrotoxicity is primarily mediated through the intrinsic pathway. In the intrinsic pathway, translocation of the BAX protein to the mitochondria triggers the release of cytochrome C to the cytoplasm, activating caspases and initiating apoptosis in cisplatin-induced nephrotoxicity [44, 56, 69–71], hepatotoxicity [72, 73], testiculotoxicity [45, 74], and ototoxicity [63, 75]. Recent studies have also shown that cisplatin triggers the expression of p53 and cytochrome C in renal tubular cells [76, 77]. Similarly, Cheng *et al*. [35] reported that carboplatin induces apoptosis in cardiomyocytes, supported by the observed upregulation of apoptotic markers like caspase-3, caspase-9, BcL-XL, and cytochrome c, by western blotting [35]. Additionally, Cetinkaya *et al*. [78] demonstrated that carboplatin alters the apoptotic balance in a gonad toxicity model.

Apoptosis has also been implicated in the mechanism of oxaliplatin toxicity. Donzelli *et al*. [62] demonstrated that both cisplatin and oxaliplatin induce apoptosis in neuroblastoma cells through the downregulation of Bcl-2, an anti-apoptotic factor, linking apoptosis to oxaliplatin-induced neurotoxicity [79]. In addition, oxaliplatin-induced peripheral neuropathy through increased caspase-3 and BAX levels, while simultaneously decreasing the anti-apoptotic Bcl-2 levels [62].

In addition to apoptosis, recent studies have also shown a correlation between cisplatin-induced apoptosis and ER stress. Reduced protein synthesis in tissues during PAC toxicity suggests the onset of ER stress due to oxidative exertion [80]. ER stress activates the unfolded protein response (UPR) pathway, leading to the synthesis of chaperones to facilitate the removal of accumulated misfolded proteins, and to downregulate protein synthesis. During ER stress, glucose-regulated protein 78 (GRP78), activating transcription factor 6 (ATF6), and CCAAT-enhancer-binding protein homologous protein (CHOP), are activated [81]. ATF6 promotes the upregulation of various pro-apoptotic genes via CHOP, which triggers caspase-3 activation and initiates apoptosis [82]. A recent study by Mentese *et al*. [80], observed significantly elevated levels of ER stress and apoptosis markers in the testicular tissues of rats treated with cisplatin [80].

Although apoptosis is a well-known form of cell death in chemical toxicity, reports suggest that PAC toxicity may also be associated with autophagy [69]. Autophagy is defined as the cellular process of digestion of organelles or excess nutrients and substrates by the lysosome [83]. Autophagy is mainly known to be mediated by the Autophagy-related 5 (Atg5) and Autophagy-related 12 (Atg12) proteins, which regulate the formation of the phagophore (a structure that engulfs the material to be digested) to form an autophagosome. The autophagosome fuses with the lysosome, within which the content is broken down by proteases [83, 84]. Trajkovic *et al*. [85] demonstrated that cisplatin-induced AMPK signaling and autophagy in renal cells, and lead to the attenuation of cisplatin-induced oxidative stress, DNA fragmentation, caspase activation, and apoptosis [85]. Similarly, Takahashi *et al*. [85] found that autophagy-deficient distal renal tubule cells exhibited higher levels of ROS and DNA damage compared with the control upon cisplatin administration [86]. In corroboration, Sun *et al*. [87] revealed that cisplatin inhibited autophagy in kidney tubule cells, promoting toxicity. All these studies seem to indicate that autophagy counteracts cisplatin toxicity. However, studies have also reported a toxic role of autophagy in mediating cisplatin side effects. Upregulated autophagy has been shown to induce both apoptosis-independent as well as apoptosis-dependent cell death, where Atg5 activates the death-inducing signaling complex (DISC) protein, which controls the activity of caspases [88]. Zhang *et al*. [89] demonstrated that cisplatin generated ROS in the intestinal tissues of mice, which promoted MAPK-dependent autophagy through the activation of autophagy-related proteins—Beclin-1 and LC33, crucial for phagophore formation. The activation of autophagy combined with elevated levels of MDA and reduced activity of SOD and CAT, resulted in the apoptosis of intestinal villous cells, causing intestinal toxicity. With contradictory studies, the role of autophagy in PAC toxicity is debatable. It has been demonstrated that a short duration exposure to cisplatin could activate cytoprotective autophagy in kidney epithelial cells [90], mediated by the upregulation of autophagy-related proteins—LC3B, Beclin-1, and p62 in cisplatin-induced nephrotoxicity [69]. However, high concentrations or chronic exposure to cisplatin may suppress autophagy and dominate apoptosis in renal cells [91]. Therefore, it is suggested that autophagy acts as double-edge sword in cisplatin toxicity, with studies supporting both protective and toxic roles, depending on the context and cell type.

## PI3K/AKT/mTOR signaling and Wnt/β-catenin pathway

While the mechanisms discussed above represent the most extensively studied and likely pathways through which PAC induces toxicity and side effects, there are additional pathways and biochemical processes that may play a role. For instance, the involvement of PI3K/AKT/mTOR (phosphoinositide 3-kinase; mammalian target of rapamycin) signaling pathway has been suggested in cisplatin toxicity, although the existing evidence is contradictory [63, 92]. Potočnjak *et al*. [69] reported that increased AKT/ERK1/2/FOXO3a signaling aggravates cisplatin nephrotoxicity [56]. Similarly, in cisplatin-induced kidney injury, significant expression of PI3K and AKT proteins has been observed [69]. However, Al-Shahat *et al*. [92] found that a downregulation in the mRNA expression of PI3K, AKT, mTOR, and PTEN (phosphatase and tensin homolog), promotes cisplatin-induced ovarian damage [92].

The Wnt (Wingless-related integration site) pathway is a signaling pathway responsible for organ development, homeostasis, and repair of tissues. In the kidneys, the Wnt/β-catenin pathway has been reported to induce nephrogenesis [93], leading to a debate about its role in protecting against cisplatin toxicity [94]. However, recent studies highlight its involvement in cisplatin toxicity. Jiao *et al*. [95] demonstrated that conditioned media derived from bone marrow mesenchymal stem cells, activated the Wnt/β-catenin pathway, providing nephroprotection against cisplatin nephrotoxicity by reducing intracellular ROS levels. However, a study by Badawy *et al*. [96] showed that Wnt/β-catenin pathway is involved in cisplatin-induced nephrotoxicity. The overall role of

this pathway in PAC toxicity may depend on the extent or duration of cisplatin exposure. In fact, one study has suggested that Wnt4 expression is considerably upregulated during the early phases of renal exposure to cisplatin [94]. However, the duration-dependent role of Wnt/β-catenin in PAC nephrotoxicity remains to be explored.

## Molecular mechanisms of ferroptosis in chemotherapy-induced toxicity

Ferroptosis, a form of iron-dependent, nonapoptotic, programmed cell death, is mechanistically linked to intracellular iron overload, lipid peroxidation, altered glutathione homeostasis, and other signaling pathways [97]. Coined by Stockwell and team [98], ferroptosis is distinct from other forms of cell death such as necrosis, pyroptosis, and apoptosis, characterized morphologically by lipid membrane degeneration, loss of mitochondrial integrity, and the absence of chromatin condensation in the nucleus [98]. Biochemically, ferroptosis is marked by reduced GSH, downregulation of GPX-4, iron accumulation, and lipid peroxide buildup [97]. At the molecular level, iron ions taken up by cells via the transferrin receptor react with mitochondrial ROS such as hydrogen peroxides, to undergo the Fenton's reaction, forming more reactive ROS such as superoxide radicals and hydroxyl radicals. These radicals target the cell and mitochondrial membranes, giving rise to lipid peroxides. The cellular antioxidant system, dependent on reduced GSH, regulates these lipid peroxides. The GPX-4 enzyme utilizes reduced GSH to convert lipid peroxides into lipid alcohols, thereby preventing membrane disruption and mitochondrial damage [99, 100]. While the balance between ROS generation and antioxidant functions is maintained under normal conditions, certain external factors, such as drug administration, can induce intracellular changes and trigger ferroptosis. These changes could be the upregulation of the transferrin receptor, inhibition of System $Xc^-$, and the downregulation of GPX-4.

### Upregulation of the transferrin receptor

The transferrin receptor located in the cell membrane facilitates the uptake of iron ions. Its expression level varies in different tissues depending on their iron requirements. Iron uptake is usually higher in the liver where it is stored in the form of ferritin, while other organs maintain a baseline level of iron [101]. However, drug administration may induce an overexpression of the transferrin receptor in nontargeted tissues, leading to intracellular iron accumulation. Subsequently, the intracellular iron may trigger ROS generation via the Fenton's reaction, which will result in increased lipid peroxidation and ferroptosis [102].

The upregulation of the transferrin receptor contributing to ferroptosis is compounded by additional intracellular alterations. For instance, ferric iron ($Fe^{3+}$) in the cytosol taken up via the transferrin receptor (CD71), generates ferrous iron ($Fe^{2+}$), that is stored as ferritin in association with the ferritin heavy chain 1(FTH-1) and ferritin light chain 1 (FTL-1). Typically, iron storage as ferritin ranges from 2000 to 4500 $Fe^{2+}$ ions. However, a lowered expression of FTH-1 and FTL-1 coupled with transferrin receptor upregulation, can lead to excessive iron build-up and lipid peroxidation, overwhelming the antioxidant system and triggering ferroptosis [103].

### Inhibition of System $Xc^-$

Glutathione (GSH), an essential component of the cellular antioxidant defense system, is synthesized through a complex process. First, glutamate exits the cell, allowing cystine to enter the cell via the glutamate-cystine transporter system, known as system $Xc^-$. Subsequently, cystine is converted to cysteine, which is further utilized in the synthesis of glutathione (GSH). Certain drugs have the potential to inhibit the function of system $Xc^-$, which may lead to a reduction in GSH levels. Consequently, this may result in the accumulation of intracellular iron-generated ROS [103, 104].

### Inhibition or downregulation of GPX-4

The GPX-4 enzyme plays a vital role in cellular antioxidant defense by converting lipid peroxides into lipid alcohols via the utilization of reduced GSH, thereby preventing the accumulation of lipid peroxides and subsequent damage to cell membranes and mitochondria [100]. Considering the importance of this enzyme for maintaining intracellular antioxidant balance, inhibition of GPX-4 by drugs can directly lead to the initiation of ferroptosis [105].

Ferroptosis can be triggered by anticancer agents through various mechanisms. While ferroptosis can serve as an effective measure for killing cancer cells, thereby enhancing chemosensitivity and overcoming chemoresistance [106, 107], it is emerging as a potentially harmful ROS-mediated process, contributing to nontarget tissue toxicity induced by anticancer drugs [18, 108, 109]. Sorafenib, a prominent tyrosine kinase inhibitor used in treatment of hepatocellular carcinoma, has been identified as a major inducer of ferroptosis [110]. Recent studies have focused on enhancing the ferroptosis mechanism of sorafenib, to improve its efficacy against cancerous hepatocytes [111–113]. However, there have also been studies that have revealed the adverse effects of sorafenib-induced ferroptosis. In a study conducted by Jiang *et al* (2022), ferroptosis was identified as a driver of sorafenib-induced cardiotoxicity [114]. Administration of sorafenib resulted in enhanced ROS production within cardiomyocytes, resulting in ER damage, followed by the UPR and eventual cell death. The role of ferroptosis was confirmed when toxicity was mitigated by the administration of ferrostatin, an important iron chelator. Additionally, overexpressing activation transcription factor 4 (ATF4) caused the upregulation of system $Xc^-$, thereby increasing GSH levels and reducing ROS levels, to attenuate the cardiotoxicity. Apart from sorafenib, doxorubicin, an anthracycline commonly administered against leukemia treatment, is often limited in its use due to its irreversible cardiotoxic effects [115, 116]. Ferroptosis has been implicated in the pathophysiology of both doxorubicin- and fluorouracil-induced cardiotoxicity [115, 117, 118]. Recently, Tadokoro *et al*. [119] observed that mice administered with doxorubicin displayed increased ROS levels and mitochondrial dysfunction in cardiomyocytes, indicating the possible role of ferroptosis [119]. There were two mechanisms proposed. First, doxorubicin may have upregulated the HO-1 enzyme, leading to increased iron levels and mitochondrial ROS generation, causing mitochondrial dysfunction. Second, doxorubicin may have downregulated the GPX-4 enzyme, resulting in lipid peroxide accumulation, and the ferroptotic death of cardiomyocytes. Although research on ferroptosis primarily focuses on potential benefits in cancer treatment, the studies mentioned above represent a subset that investigates

ferroptosis as a mechanism of toxicity of anti-cancer agents. From this perspective, the aim of the subsequent sections of this review is to analyze ferroptosis as a toxicity mechanism of PAC drugs, along with the exploration of natural product mitigation strategies. Understanding the role of ferroptosis in PAC toxicity is quite promising, since oxidative stress, a downstream consequence of ferroptosis, is an established mechanism in PAC-induced toxicity.

## Ferroptosis in PAC-induced toxicity

Recently, the understanding of PAC-induced toxicity at the molecular level has been significantly advanced through exploration from multiple lenses, such as signaling pathways, oxidative stress, apoptosis, and autophagy, as extensively discussed in previous sections. With the increasing importance of ferroptosis and its investigation as a mechanism of toxicity induced by anti-cancer agents, efforts are underway to determine whether ferroptosis is also implicated in PAC toxicity. This is crucial since PAC drugs exhibit high potency, but are often limited in their use due to their widespread toxicity. Therefore, the more we understand the underlying mechanisms, the better we can modulate them for cancer treatment.

### Ferroptosis in cisplatin toxicity

Ferroptosis has emerged as a promising target in cancer therapy. Cisplatin induces ferroptosis either directly or in combination with an adjuvant, to promote cytotoxicity in cancer cells [120–122]. However, ferroptosis also plays a detrimental role in the development of cisplatin-induced toxicities [103, 123, 124]. In an earlier study by Baliga et al. [125], the role of iron in mediating the nephrotoxic effect of cisplatin was investigated both *in vitro* and *in vivo*. The results of *in vitro* experiments indicated that cisplatin-induced cytotoxicity in renal epithelial cells (LLC-PK1) by an exaggerated release of bleomycin-detectable iron. Interestingly, treatment with iron chelators such as deferoxamine and 1,10-phenanthroline, mitigated cisplatin cytotoxicity in LLC-PK1 cells. Similar findings were reported by Ikeda *et al.* [18], where there was a substantial increase in the bleomycin-detectable iron content in the kidneys of rats who were treated with cisplatin. The study further reported the direct role of ferroptosis in cisplatin-induced nephropathy, where cisplatin administration in mice upregulated the transferrin receptor and increased mRNA levels of ferroptosis markers such as cyclooxygenase-2 (COX-2), 4-hydroxynonenal (4-HNE), and ferritin. Additionally, cisplatin led to elevated levels of renal ferrous ions ($Fe^{2+}$) and hydroxyl radicals, coupled with a decrease in the expression of GPX-4. These effects were attenuated by iron chelators. The study of Hu *et al.* [103] revealed the crucial anti-ferroptotic role of Nrf2 in an acute kidney injury (AKI) mouse model induced by cisplatin [103]. In the study, it was found that Nrf2 deletion markedly upregulated the expression of ferroptosis-related genes and aggravated cisplatin-induced AKI by promoting iron accumulation *in vivo*. Interestingly, Nrf2 activation *in vitro* was shown to prevent iron accumulation and downstream ferroptosis events in siNrf2-treated cells. Inhibition of GPX-4 has also been implicated in cisplatin-induced toxicity. GPX-4 depends on GSH and plays a protective role against ferroptosis by modulating intracellular redox homeostasis. Therefore, depletion in cellular GSH and/or GPX-4, induces ferroptosis by promoting a build-up of lipid hydroperoxides and other toxic lipid ROS. In a study conducted by Hu et al. [124], ferroptosis induction in the kidneys of mice due to cisplatin administration was confirmed through the downregulation of the GPX-4 enzyme. Additionally, pre-administration of ferrostatin-1, a well-known ferroptosis inhibitor, showed decreased levels of blood urea nitrogen when compared with the cisplatin administration group. Besides exploring the role of ferroptosis in cisplatin-induced nephrotoxicity, the study further investigated whether the vitamin D receptor, known to mitigate nephrotoxicity, did so by inhibiting ferroptosis. The finding of the study reported that the expression of the vitamin D receptor enhanced the levels of GPX-4, and reduced the accumulation of malondialdehyde (MDA). Overall, the study provided crucial evidence regarding ferroptosis as a mechanism of cisplatin toxicity, while recognizing the potential of modulating the vitamin D receptor for a nephroprotective effect. Cisplatin-induced ferroptosis, which leads to nephrotoxicity, has also been linked to the suppression of system $Xc^-$. Yu *et al.* [126] reported that cisplatin suppressed system $Xc^-$ transporter activity by inhibiting SLC7A11, resulting in the depletion of GPX-4 in HK2 cells in a dose-dependent manner. The study further reported that cisplatin administration upregulated the junction protein Cx43, which subsequently inhibited SLC7A11. These findings provide a robust mechanistic explanation, supported by evidence demonstrating decreased toxicity upon the administration of a Cx43 inhibitor, gap27.

In addition to its role in cisplatin-induced nephrotoxicity, a study by Mei *et al.* [127] highlighted ferroptosis as a mechanism of cisplatin-induced ototoxicity. Cisplatin treatment caused an increase in iron levels, ROS, and lipid peroxidation in mouse auditory cell lines (HEI-OCI) and cochlear hair cells. The effects were significantly mitigated by a ferroptosis inhibitor, ferrostatin-1. Similarly, Jian *et al.* [109] demonstrated that ferroptosis induced in the cochlea of cisplatin-treated mice was dependent on autophagy, and resulted in hearing loss, which was inhibited by ferrostatin-1 and chloroquine (autophagy inhibitor) [109]. Further, the study identified GPX-4 inhibition and system $Xc^-$ inhibition as mechanisms by which cisplatin triggered ferroptosis and induced ototoxicity. The identification of the involvement of ferroptosis in cisplatin-triggered ototoxicity has facilitated therapeutic interventions. In a study conducted by Niu *et al.* [128], the findings suggested that cisplatin-induced damage in cochlear hair cells of mice through alterations in the levels of SLC7A11 and GPX-4. These effects were associated with the Hippo/YAP pathway, as cisplatin administration also resulted in YAP downregulation. Treatment with LAT1-IN-1, a YAP activator, restored SLC7A11 and GPX-4 expression levels, mitigating ototoxicity. A study by Zhang *et al.* [129] revealed a relatively unexplored effect of cisplatin-induced ovarian damage. Cisplatin significantly reduced ovarian volume, primordial and antral follicle counts, and induced ovarian fibrosis. This damage was attributed to cisplatin-induced ferroptosis, characterized by increased ROS production and mitochondrial lipid peroxidation. N-acetylcysteine administration attenuated ovarian toxicity by promoting GPX-4, Nrf2, and HO-1 expression. Recent studies by Gu *et al.* [122], revealed that cisplatin induces ferroptosis in both nonsmall cell lung cancer cells and fibrosarcoma cell lines by inhibiting

GPX-4 and reducing GSH levels. The study provides insight into the role of cisplatin in triggering ferroptosis in cancer cells, offering a therapeutic perspective, beyond its known toxic effects such as nephrotoxicity, ototoxicity, and ovarian damage.

### Ferroptosis in carboplatin toxicity

The role of carboplatin in inducing cytotoxicity has been explored extensively, covering aspects such as DNA damage, apoptosis, ROS generation, and signaling pathway inhibition, as discussed in the previous sections. However, based on the existing literature, the involvement of carboplatin in inducing ferroptosis has neither been reported as a mechanism against cancer cells nor as a toxicity mechanism in nontarget tissues. However, recently, Yang *et al.* [130] reported that mice injected with carboplatin initially underwent a reduction in tumor growth, however, subsequently developed resistance and a reduced response to erastin-induced ferroptosis [130]. This phenomenon was attributed to the carboplatin-induced downregulation of TAZ, a transcription factor that promotes the expression of an angiopoietin protein required for NOX2 uptake, crucial for ferroptosis. This shows that while carboplatin is unlikely to employ ferroptosis as a mechanism of action or toxicity, it may interfere with the ferroptosis process, leading to resistant phenotypes. On the contrary, there are reports of carboplatin-resistant cancer cells being effectively targeted by ferroptosis inducers. In a recent study by Liu *et al.* [131], carboplatin-resistant retinoblastoma cells were treated with 4-octyl itaconate, which induced autophagy-dependent ferroptosis, leading to the eradication of the tumor cells [131]. Overall, there are very limited studies exploring the relationship between carboplatin and ferroptosis, and the existing investigations are superficial and inconsistent, offering minimal insights into ferroptosis as a mechanism of action or toxicity of carboplatin.

### Ferroptosis in oxaliplatin toxicity

Similar to cisplatin, oxaliplatin has also been investigated for its potential to induce ferroptosis in various contexts. Studies have reported both beneficial and detrimental effects resulting from oxaliplatin-induced ferroptosis. Oxaliplatin has shown promising therapeutic response against aggressive colorectal cancer through ferroptosis. Recently, Liu and Wang [132] demonstrated that oxaliplatin-induced ferroptosis in a colorectal cancer cell line HT29, by inhibiting Nrf2. While oxaliplatin exhibiting inhibitory activity against colorectal cancer via ferroptosis is a positive aspect, oxaliplatin-induced ferroptosis it is also associated with ototoxicity, presenting a drawback. Xu et al. [133] recently reported oxaliplatin-induced ferroptosis in cochlear hair cells, OC1, through altered expression of Nrf2, as well as downstream antioxidant elements such as HO-1 and GPX-4. Given the strong link between oxaliplatin and Nrf2 as a trigger for ferroptosis, a clinical study has been conducted [134]. In the study, oxaliplatin was observed to cause peripheral neuropathy through Nrf2 inhibition and subsequent ferroptosis induction in 65 patients receiving the FOLFOX regimen for colorectal cancer. Furthermore, the administration of L-carnosine restored Nrf2 expression, demonstrating neuroprotective effects in the patients. Besides Nrf2 inhibition, studies have reported system $Xc^-$ inhibition resulting in decreased intracellular GSH levels, in oxaliplatin-induced hepatotoxicity [37]. Earlier studies by Kobayashi *et al.* [135] and Kawashiri *et al.* [136], reported that the oral co-administration of cysteine and theanine had a neuroprotective effect in patients with chronic peripheral neuropathy resulting from oxaliplatin administration. This combination facilitated the conversion of cystine and theanine into cysteine and glutamate intracellularly, potentially compensating for the low GSH levels and reducing oxidative stress.

Although ferroptosis has been extensively explored as a mechanism of action of oxaliplatin against cancer cells, as well as a mechanism of oxaliplatin-induced toxicity, there could be other mechanisms beyond Nrf2 and system $Xc^-$ inhibition in mediating the ferroptotic toxicity. Therefore, further comprehensive studies are crucial for understanding how cisplatin, carboplatin, and oxaliplatin trigger ferroptotic toxicity to develop effective therapeutic interventions.

## Natural products as modulators of ferroptosis in PAC-induced toxicity

Studies have indicated that ferroptosis is involved in the pathogenesis of PAC-induced toxicity. Therefore, it is crucial to introduce therapeutic interventions to mitigate ferroptosis in PAC toxicity. Systematic research has been carried out to explore ferroptosis inhibitors that could reduce PAC-induced side effects. Some well-established ferroptosis inhibitors include ferrostatin-1, α-tocopherol, and liproxstatin-1 [137]. Researchers have investigated natural product ferroptosis inhibitors for their ability to scavenge ROS, break free radical chains, and enhance the expression of molecular antioxidants [138]. The molecular effects of such natural products have been reviewed in this section (Fig. 3; Table 1).

### Natural products with iron chelation mechanism

Ferroptosis can be triggered within a cell by multiple factors, including the upregulation of the transferrin receptor, downregulation of system $Xc^-$, glutathione depletion, and others. When the transferrin receptor is overexpressed, it leads to increased iron uptake by the cells. This excess iron promotes the generation of ROS through Fenton's reaction, ultimately causing ferroptosis [161]. In situations where elevated intracellular iron levels drive ferroptosis, iron chelators or iron-binding compounds are commonly used as inhibitors, since they possess the ability to enter cells and bind to iron ions, further preventing them from reacting with hydrogen peroxides to generate ROS. Some natural products such as quercetin, baicalein, and resveratrol, are known to inhibit ferroptosis through this mechanism [162].

Quercetin, a common flavonoid found in various fruits and vegetables, has demonstrated potential in mitigating cisplatin-induced nephrotoxicity across multiple studies [139–142]. Sanchez-Gonzales *et al.* [142] showed that the preadministration of mice with quercetin not only reduced serum creatinine levels, but also lowered renal oxidative stress, as indicated by an elevated level of reduced GSH in quercetin pretreated mice compared with mice treated with cisplatin alone [142]. Similarly, Ilić *et al.* (2014) [139] showed that mice provided with intraperitoneal injections of cisplatin developed focal apoptosis in proximal tubulocites. However, this impact was mitigated in mice administered with quercetin, which showed improvement in serum creatinine and urea levels that were notably elevated in cisplatin-treated mice.

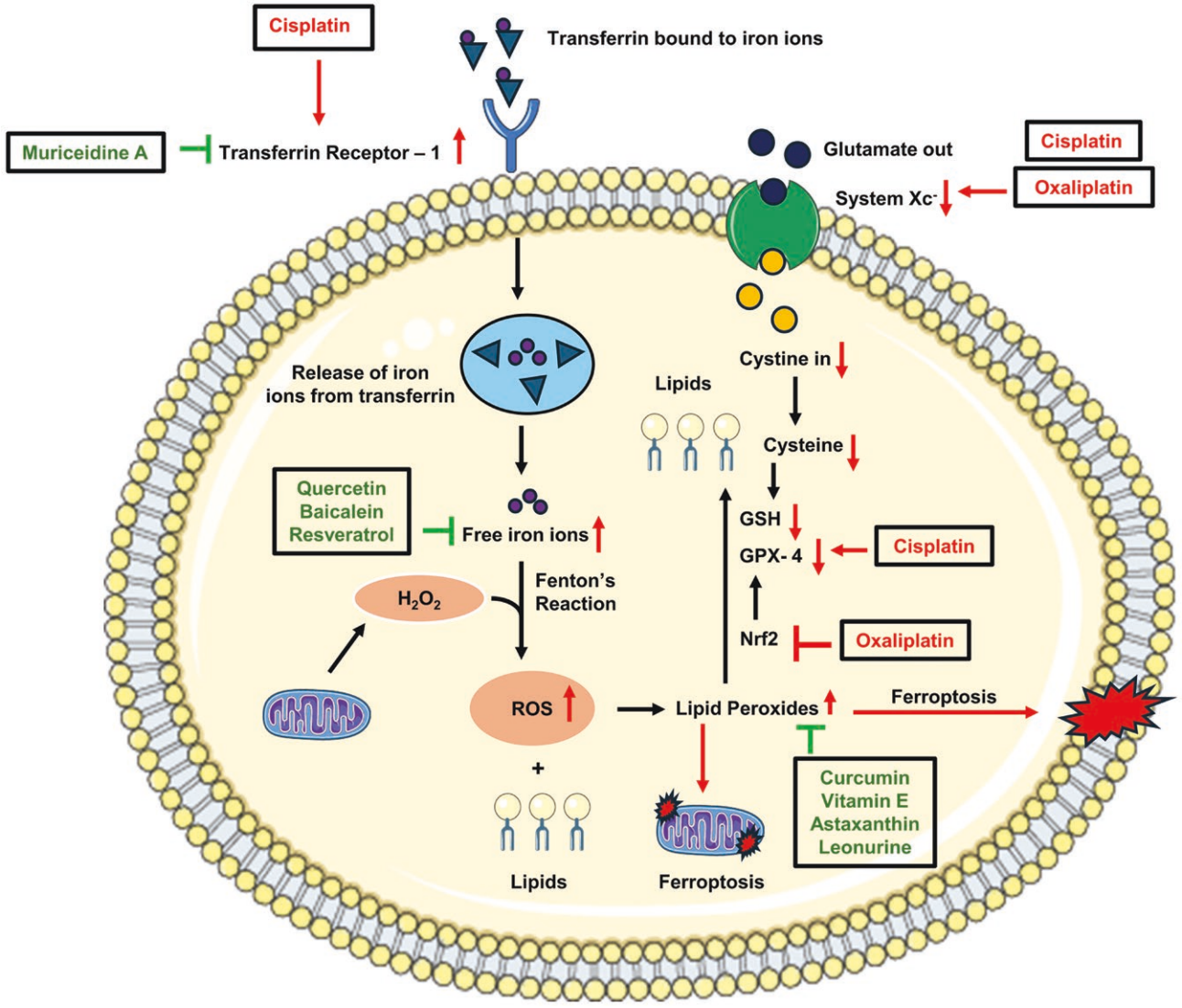



**Fig. 3.** Molecular mechanisms of PAC-induced ferroptosis and mitigation mechanisms by natural products.

Additionally, cisplatin-induced elevation in MDA levels was also significantly reduced by quercetin, suggesting a reduction in lipid peroxidation that conferred nephroprotection. Algandaby [143] revealed the role of quercetin in attenuating cisplatin-induced ovarian damage through anti-apoptotic, anti-inflammatory, and antioxidant mechanisms. Quercetin was observed to prevent GSH depletion, GPX-4 exhaustion, and MDA accumulation in the ovaries of mice, which are relevant antioxidant mechanisms for preventing ferroptosis.

Baicalein, a flavonoid isolated from the roots of *Scutellaria baicalensis*, is a well-established antioxidant and anti-inflammatory agent [163]. A recent study by Xie *et al.* [164] reported that baicalein chelated iron and inhibited erastin-induced ferroptosis in a pancreatic cancer cell line. The iron chelation potency was comparable to other synthetic iron chelators tested in the form of ferrostatin-1 and deferoxamine mesylate. The study also demonstrated the ability of baicalein to attenuate various ferroptosis markers in the form of iron and MDA levels, as well as the suppression of GPX-4 degradation. Recently, Sahu *et al.* [144] assessed the effect of baicalein in cisplatin-treated mice models. Cisplatin-induced nephrotoxicity by triggering alterations in kidney histology, biochemical parameters, inflammatory cascades, and antioxidant defenses. However, administration of baicalein reduced cisplatin toxicity, primarily through the restoration of antioxidant defenses in the form of SOD, CAT, and GSH levels. In corroboration, Sawant *et al.* [145] validated the nephroprotective effect of baicalein against cisplatin-induced nephrotoxicity, and highlighted its role in attenuating Nrf2 expression and mediating protective antioxidant effects. Baicalein has also been studied for its ability to ameliorate cisplatin-induced hepatotoxicity. Niu *et al.* [146] observed that baicalein administration restored liver function parameters such as serum alanine and alkaline phosphatase levels, and enhanced the expression of GPX-4, SOD, and CAT enzymes, while reducing MDA levels in the liver.

Resveratrol is a natural compound that has been extensively studied for its potential in managing PAC-induced nephrotoxicity, ototoxicity, and damage to other organs such as the heart or nervous system [147, 165, 166]. Valentovic *et al.* [147] investigated the role of resveratrol in mitigating cisplatin-induced nephrotoxicity in a mouse model, where

pretreatment with resveratrol reduced oxidative stress in kidneys by restoring the activity of GPX-4 and SOD enzymes while lowering the levels of 4-HNE. Recent research by Kato *et al*. [148] employed density functional theory computation analysis, and revealed that resveratrol does not form stable iron chelates, and rather forms complexes with iron ions, thereby hindering their involvement in Fenton's reaction to prevent ferroptosis. The study further reported the neuroprotective

**Table 1.** Natural product modulators of ferroptosis in PAC-induced toxicity.

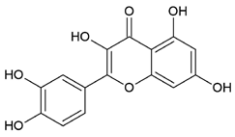
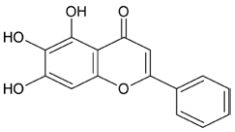
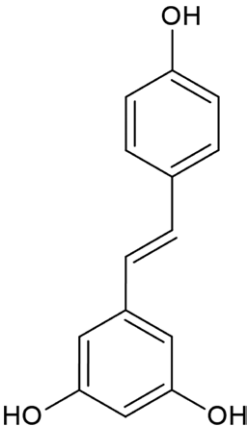
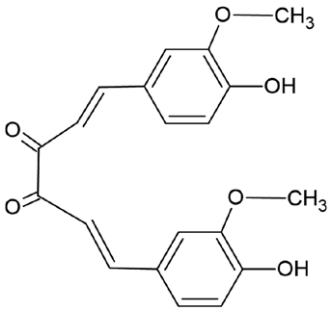
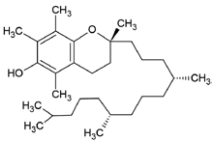
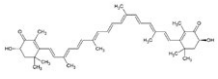
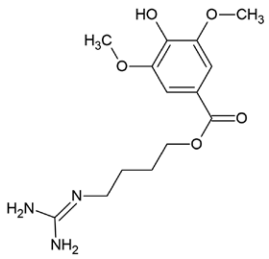
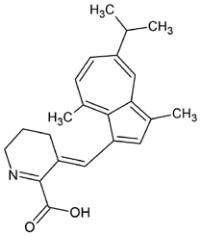
| Natural product | Chemical structure | Model | Alterations in ferroptosis markers | References |
|---|---|---|---|---|
| Quercetin |  | Mice | GSH↑, GPX-4↑, MDA↓ | [139–143] |
| Baicalein |  | Mice | SOD↑, CAT↑, GPX-4↑, GSH↑, MDA↓, Nrf2↑ | [144–146] |
| Resveratrol |  | Mice, *in silico* model | GPX-4↑, SOD↑, $Fe^{2+}$↓ | [147, 148] |
| Curcumin |  | Mice, rabbits | GSH↑, SOD↑, CAT↑, MDA↓, TNF-α↓ | [149–152] |
| Vitamin E |  | Mice, rats | MDA↓ | [153–155] |
| Astaxanthin |  | Mice, rats | GSH↑, MDA↓, Nrf2↑ | [156–159] |

**Table 1.** Continued

| Natural product | Chemical structure | Model | Alterations in ferroptosis markers | References |
|---|---|---|---|---|
| Leonurine |  | Mice and HK-2 cells | $Fe^{2+}$↓, Nrf2↑, GPX-4↑ | [103] |
| Muriceidine A |  | MDA-MB-231, K562, HeLa, and HCT-116 cells | Tfr1 Inhibition | [160] |

role of resveratrol against oxaliplatin-induced neurotoxicity through the highlighted iron-binding mechanism [148]. This finding of resveratrol's ability to form iron complexes reveals a new aspect of its mechanism beyond its well-established antioxidant functions, which potentiates its application against other targets of PAC toxicity, beyond the nervous system.

While numerous studies focus on the protective effect of quercetin, baicalein, and resveratrol against PAC-induced toxicity by modulating various ferroptosis markers, they do not specifically address their well-established iron chelation mechanism in mitigating PAC-induced toxicity. Furthermore, the studies do not highlight their anti-ferroptosis functions exclusively from their antioxidant effects. Therefore, conducting more specialized studies into understanding the anti-ferroptosis mechanisms of these natural products in the context of PAC-toxicity mitigation, would strengthen their potential utility as adjuvants. In addition, elevated iron levels have been implicated in various PAC-induced toxicities, such as nephrotoxicity [167] and ototoxicity [109]. While synthetic iron chelators like deferoxamine and deferiprone have been explored to mitigate these toxic effects, their efficacy has been shown to be limited [168]. This highlights the significance of exploring alternative iron chelators or iron-binding compounds like quercetin, baicalein, or resveratrol, for reducing the toxic effects of PAC-induced ferroptosis. Moreover, there are very limited studies exploring the use of iron chelators against ferroptosis induced by other PAC drugs such as oxaliplatin and carboplatin. Hence, there is a critical need to investigate the potential of the discussed iron chelators against ferroptotic damage induced by these PAC drugs.

## Natural products as inhibitors of lipid peroxidation

Natural products such as ferroptosis inhibitors, also possess the ability to prevent damage induced by iron-generated ROS, by scavenging lipid peroxyl radicals. These natural products function by halting the initiation of a chain reaction that results in the accumulation of lipid peroxides and causes damage to the cell membrane and mitochondria as a part of ferroptosis [169]. Some of these ferroptosis inhibitors that reduce lipid peroxide levels, include curcumin, vitamin E, astaxanthin, and leonurine [170].

Curcumin is a very well-known antioxidant that has been established as an adjuvant for mitigating cisplatin-induced nephrotoxicity. Kuhad *et al.* [149] demonstrated that pretreatment with curcumin restores renal function in cisplatin-treated mice, as indicated by the normalization of key biochemical parameters of kidney function [149], as well as significantly lowered lipid peroxide levels through increased GSH and SOD activity for ferroptosis inhibition. El-Gizawy *et al.* [150] reported that curcumin can effectively mitigate cisplatin-induced hepatotoxicity by reducing MDA and TNF-α levels in the liver of mice. Curcumin has also shown a promising effect in preventing carboplatin-induced myelotoxicity in mice models [151]. The study reported that carboplatin treatment enhanced MDA levels, decreased GSH levels, and caused DNA damage, which was reversed to the normal range by curcumin treatment. Furthermore, Kandemir *et al.* [152] demonstrated that curcumin can mitigate cisplatin-induced testicular toxicity, based on the observed elevation in GSH levels and enhanced expression of CAT and GPX enzymes, in a rabbit model.

Vitamin E is a fat-soluble vitamin, and astaxanthin is a carotenoid pigment found extensively in plants, algae, and seafood. Both vitamin E and astaxanthin function through a similar mechanism of action, where they scavenge lipid peroxyl radicals and prevent the build-up of lipid peroxides, which are major mediators of ferroptosis [171]. Vitamin E has demonstrated efficacy in mitigating cisplatin-induced nephrotoxicity by reducing lipid peroxidation [153–155], while

astaxanthin has been shown to prevent lipid peroxidation and promote Nrf2 signaling for an antioxidant effect [156]. Studies have reported that astaxanthin can effectively attenuate cisplatin-induced ototoxicity [157], nephrotoxicity [158], and retinotoxicity [159]. Kinal *et al*. [157] evaluated the protective effect of astaxanthin against cisplatin-induced ototoxicity in rats. The rats subjected to cisplatin treatment exhibited reduced auditory function, and low antioxidant levels overall. Treatment with astaxanthin (40 mg/kg) reversed the observed effects. Findik *et al*. [159] investigated the occurrence of retinotoxicity induced by cisplatin. It was reported that cisplatin administration in mice led to elevated markers of interstitial fibrosis, increased levels of MDA, and decreased levels of GSH in retinal tissue, which were mitigated by astaxanthin treatment. A major factor contributing to the growing interest in astaxanthin, is its higher potency compared with the conventional antioxidant vitamin E, in addition to its potential as a valuable adjuvant for mitigating drug-induced toxicity [172].

In recent years, the therapeutic potential of leonurine in mitigating PAC-induced toxicity has gained significant attention. Leonurine, a major alkaloid compound derived from motherwort, has been extensively studied for its pharmacological properties, particularly its ability to inhibit lipid peroxidation and oxidative stress in various pathological conditions. A recent investigation reported that leonurine was effective in preventing ferroptosis in cisplatin-induced nephrotoxicity, by inhibiting iron accumulation and lipid peroxidation through Nrf2 activation and the upregulation of GPX-4 expression [103]. Moreover, the study demonstrated that Nrf2 knockout ($Nrf2^{-/-}$) mice were more susceptible to ferroptotic damage following cisplatin-induced acute kidney injury, compared with control mice.

Overall, natural products that hinder ferroptosis by inhibiting lipid peroxide synthesis play a crucial role in regulating PAC-induced toxicity, as evidenced by numerous studies conducted in recent times. However, similar to iron chelators, natural products targeting lipid peroxidation in PAC-toxicity too, have been primarily evaluated for their antioxidant functions and modulation of ferroptosis markers. This limited understanding of their anti-ferroptosis mechanisms often creates a barrier to their clinical adoption as PAC adjuvants. Hence, with a more comprehensive understanding of the holistic mechanistic impacts of the discussed natural products on the body, their potential as PAC adjuvants can be explored at the clinical level.

### Natural products in transferrin receptor inhibition

Transferrin receptor plays a pivotal role in cellular iron uptake, facilitating the entry of iron ions bound to transferrin proteins into the cells. Once inside, the iron ions are released and utilized for various biological functions and are also stored in the form of ferritin. An upregulation of the transferrin receptor can cause excessive iron uptake, leading to ferroptosis [161]. Hence, inhibiting the transferrin receptor holds potential for the prevention of ferroptosis, but there are currently very few naturally derived inhibitors that have been studied for targeting transferrin receptors. Wu *et al*. [160] recently reported a marine natural metabolite called Muriceidine A for its potential role in targeting transferrin receptor 1 (Tfr1), causing iron depletion and reduction in ROS levels. Muriceidine A has not been fully characterized as a ferroptosis inhibitor yet, and detailed investigations into its activity can play a crucial role in regulating ferroptosis and further mitigating PAC toxicity.

## Research gaps and future perspectives

Extensive literature has thoroughly characterized the mechanism of PAC drugs beyond DNA crosslink formation, including their molecular toxicity. Drugs like cisplatin, oxaliplatin, and carboplatin have well-documented toxicity profiles. Recent studies suggest that ferroptosis might be a significant mechanism underlying PAC-induced toxicity. However, detailed investigations are crucial to fully establish the role of ferroptosis in PAC-induced toxicity. Currently, research on ferroptosis in severe carboplatin-induced toxicities, such as cardiotoxicity, is limited and requires further exploration.

Further, diverse natural products have shown promising results in mitigating PAC-induced ferroptosis. However, the precise mechanism by which they mediate their effects is not fully understood. In-depth mechanistic studies are needed to clarify these processes and potentially establish the utilization of these natural compounds as effective adjuvants in reducing PAC toxicity. Addressing these research gaps and exploring the potential of natural products can lead to the development of novel strategies to mitigate PAC toxicity. Additionally, natural compounds with ferroptosis-inhibiting properties offer promising potential as adjuvants to overcome the toxicity associated with PAC drugs, which currently pose a significant obstacle to effective cancer treatment.

## Conclusion

This review provides insights into recent advancements in understanding the toxicity mechanisms of PAC drugs, focusing on the potential involvement of ferroptosis. Ferroptosis emerges as a key mechanism contributing to the adverse effects of PAC drugs. Evidence suggests that cellular iron overload, ROS generation, and lipid peroxidation, are pivotal features of iron-dependent ferroptosis in PAC-induced toxicity. Several well-known antioxidant and anti-inflammatory natural compounds have shown anti-ferroptotic effects via diverse mechanisms—inhibition of iron accumulation, lipid peroxidation, and suppression of transferrin receptors. However, although natural compounds have shown promise in alleviating PAC-induced ferroptotic toxicity, further mechanistic studies are warranted to elucidate their potentials in modulating PAC-induced ferroptosis and assess their viability as PAC adjuvants.

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## Author contributions

A.C.F. and N.M.P. wrote the manuscript. A.C.F. and S.P. conceptualized, edited, and revised the manuscript.

## Conflict of interest

The authors have no relevant financial or non-financial interests to disclose.

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## Data availability

No datasets were generated or analyzed during the current study.

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