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REVIEW ARTICLE

Harnessing Nature: The Role of Medicinal Plants in Alleviating Cisplatin Toxicity

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A B S T R A C T

Cisplatin (CIS), a widely used chemotherapeutic agent, is often restricted by its severe side effects, including nephrotoxicity, hepatotoxicity, cardiotoxicity, and neurotoxicity. This review explores the potential protective effects of nine natural plants and their bioactive compounds against CIS-induced toxicity. Specifically, we examine the evidence for nine herbal plants, Artemisia, Cinnamon, Curcumin, Ginger, Garlic, Ginseng, Lycopene, Moringa, and *Nigella sativa* in alleviating CIS's damaging effects. These plants have been used for centuries in herbal remedies and offer several pharmacological qualities, including anti-inflammatory, anti-apoptotic, and antioxidant effects. This review summarizes the current preclinical evidence demonstrating the protective mechanisms of these natural agents against CIS toxicity, focusing on their impact on oxidative stress, inflammatory reactions, and apoptosis pathways. This review explored the potential of natural compounds as adjunctive therapies to alleviate CIS-induced toxicity. However, it also highlighted substantial research gaps, such as the necessity for thorough clinical validation, optimized dosage protocols, evaluation of synergistic effects, and a deeper understanding of the precise mechanisms of action of bioactive components. To establish scientifically validated, plant-based interventions for cancer patients, future research must address these critical gaps.

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INTRODUCTION

The extensive use of CIS, a powerful chemotherapeutic agent, is often limited by its adverse effects, including nephrotoxicity, hepatotoxicity, cardiotoxicity, reproductive complications, and ototoxicity (Ijaz *et al*., 2023). Although highly effective in treating various cancers, these toxic side effects can result in dose reductions, treatment discontinuation, and a diminished quality of life for patients. For centuries, herbal plants have been integral to traditional medicine for preventing and managing numerous health conditions, including those related to cancer therapy. Research suggests that many of these plants possess antioxidant, anti-inflammatory, and anti-apoptotic properties, which may help counteract CIS-induced toxicity (Dasari *et al*., 2022). This review aims to consolidate existing studies on the protective effects of nine medicinal plants against CIS toxicity, highlighting their potential role in mitigating the adverse effects of cisplatin treatment. By exploring the mechanisms underlying their therapeutic benefits, this review seeks to provide a comprehensive overview of current knowledge and suggest avenues for future research.

Overview of CIS: A platinum-based chemotherapy medication, cisplatin (CIS) is commonly used to treat a variety of malignancies, such as those of the testicles, ovaries, bladder, lungs, head and neck, and cervical region (Elkomy *et al*., 2020; Elsayed *et al*., 2021; Alsoudany *et al*., 2023). It stops cancer cells from dividing and proliferating by causing damage to their DNA. When researching how electric currents affect bacterial growth,

biophysicist Barnett Rosenberg of Michigan State University discovered CIS in 1965. He observed that some bacteria stopped dividing when they were exposed to platinum electrodes. This led to the isolation of the active compound, which was initially named cis-diamminedichloroplatinum (II), later abbreviated to CIS (Hoeschele, 2014). The first human trials began in 1971, led by oncologist Lawrence Einhorn at Indiana University, USA. When combined with vinblastine and bleomycin, CIS successfully treated advanced testicular cancer, a previously untreatable condition, curing over 90% of patients. Einhorn received the Lasker Award in 1978 for this innovation, which transformed cancer treatment (Hanna and Einhorn, 2014). The creation of other platinum-based medications, such as carboplatin and oxaliplatin, which have distinct qualities and adverse effects, was made possible by CIS, which has since become a common treatment for several cancers. CIS's development paved the way for the creation of subsequent platinum-based chemotherapy, including carboplatin and oxaliplatin, which exhibit unique pharmacological profiles and adverse effect spectra and have become integral components of cancer treatment regimens.

Cisplatin's mode of action: As illustrated in Fig. 2, an overview on the mechanisms of action of cisplatin-induced toxicity.

Uptake of cisplatin by cells: CIS mostly enters cells by passively diffusing across the cell membrane, shifting from a region outside the cell where its concentration is higher to one within the cell where it is lower. However, this alone does not fully explain its efficient uptake (Eljack *et al*., 2014). Research has shown that copper transporters, particularly copper transporter 1 (CTR1), facilitate CIS's entry into cells. While CTR1 primarily transports copper ions while, it also has a robust affinity for CIS. Additionally, Eljack *et al*. (2014) reported that CIS entrance is mediated by other membrane transporters, including organic cation transporters and organic cation/carnitine transporters. After entering the cell, through its interactions with nucleophiles such as proteins, DNA, and glutathione (GSH), CIS undergoes biochemical modifications and forms covalent adducts. When it binds to DNA, transcription and replication are disrupted, which results in cell death (Mezencev, 2014). Endocytosis, a mechanism by which cells absorb extracellular substances and create vesicles that carry CIS into the cytoplasm, is another way that CIS might enter cells (Zhou *et al*., 2022).

DNA adduct formation: CIS enters the cell and travels to the nucleus, where it goes through a process called aquation, in which water molecules take the place of its chloride ligands. This reaction occurs due to the high-water concentration in the nucleus. The purine bases guanine and, to a lesser extent, adenine are specifically targeted by CIS in its aqueous form as it forms covalent connections with DNA. Usually, the medication attaches at guanine's N7 position, although it can also bind at adenine's N3 position (Johnstone *et al*., 2013). In DNA, CIS creates crosslinks between and within strands. When CIS binds adjacent guanine residues on the same DNA strand, it creates an intrastrand crosslink; when it binds guanine residues on opposite DNA strands, it creates an interstrand crosslink, which causes both strands to covalently link. These adducts distort the DNA helix, causing bending and unwinding, and disrupting critical cellular processes. CIS-induced DNA damage interferes with replication and transcription, leading to cell cycle stoppage and apoptosis, which contribute to its anticancer effects (Wang *et al*., 2010).

Pathways for cell death induction: CIS triggers DNA damage by forming covalent DNA adducts, initiating the DNA damage response. Additionally, it creates reactive oxygen species (ROS) and depletes cellular antioxidants like glutathione (GSH), which leads to oxidative stress. Additionally, ROS harm proteins, lipids, and DNA, which leads to cellular malfunction and apoptosis (Abdelhamid *et al*., 2022). Oxidative stress activates inflammatory pathways, such as the NF-κB and NLRP3 inflammatory pathways, which produce pro-inflammatory cytokines and chemokines. These recruit immune cells, exacerbating inflammation and tissue damage while impairing repair mechanisms (Zohny *et al*., 2022). The oxidation process is especially pronounced in malignant cells, which become more susceptible to CIS's cytotoxic effects compared to non-malignant cells, which show fewer metabolic changes (Wang *et al*., 2021). Pro-apoptotic substances are released as a result of CIS's impact on mitochondrial activity. This includes calcium imbalance, oxidative stress, and mitochondrial DNA damage, all of which cause the outer membrane of the mitochondria to permeate and release cytochrome c and other apoptotic components. Caspases are triggered, causing apoptosis (Zhang, 2019).

Oxidative stress plays a significant role in the process of tissue damage. It occurs when an imbalance between the production of reactive oxygen species (ROS) and the body's ability to neutralize or repair their harmful effects arises (Aboubakr *et al*., 2023a; Aboubakr *et al*., 2023b; Elsayed *et al*., 2024).

In addition to apoptosis, CIS can induce necroptosis, a regulated form of cell death characterized by proteins such as RIP1, RIP3, and MLKL, which orchestrate the process. In the kidneys, CIS accumulation activates necroptosis in renal proximal tubules, amplifying local inflammation and tissue damage (Alassaf and Attia, 2023). CIS can also cause mitotic catastrophe, a form of cell death that occurs during mitosis when DNA damage disrupts normal cell cycle progression. Furthermore, CIS has been linked to ferroptosis, a newly identified form of cell death that differs from apoptosis and necrosis. Severe DNA damage caused by CIS destabilizes the tumor genome, generating immunogenic DNA fragments that trigger ferroptosis. A combination of CIS and ferroptosis inducers has been shown to augment its anticancer effects, offering a promising strategy for improving treatment outcomes (Takahashi *et al*., 2023).

Challenges in CIS-based treatment: A major challenge in CIS treatment is the progress of resistance in tumor cells. This resistance occurs through several mechanisms, such as increased DNA repair efficiency, reduced drug accumulation, and enhanced detoxification pathways. Cancer cells may also utilize translesion DNA synthesis to bypass CIS-induced DNA damage, allowing them to survive treatment (Ali *et al*., 2022).

Organs affected by the toxicity of CIS: as shown in Fig. 1, an overview of the impact of cisplatin-induced toxicity in different organs.

Kidney: Because the kidneys are responsible for excreting the medicine, CIS-induced renal damage is a serious problem. As CIS is filtered and excreted, it accumulates in the renal tubules, particularly affecting the proximal tubular cells. These cells use transporters such as the copper transporter CTR-1 to absorb CIS. After entering, CIS is aquated, resulting in reactive intermediates that damage and stress cells. Proximal tubular cells are eventually harmed as a result of mitochondrial malfunction, oxidation process, inflammatory reactions, and the progress of cell apoptosis pathways. The kidney damage also triggers an inflammatory response with cytokine release and immune cell recruitment, further intensifying renal injury. Additionally, CIS can cause vasoconstriction in the renal blood vessels, reducing blood flow and causing renal ischemia. Numerous studies have documented CIS's nephrotoxic effects and protective effects of L-Carnitine (Elkomy *et al*., 2020), lycopene and N-acetylcysteine (Elsayed *et al*., 2021), and Lebanese Cannabis sativa L. extract (Khalil *et al*., 2025).

Liver: The liver, responsible for detoxification, is susceptible to CIS-induced toxicity, though less commonly than the kidneys. When liver damage occurs, it can result in hepatocellular injury and elevated liver enzyme levels (Elsayed *et al*., 2021). By producing reactive oxygen species (ROS), CIS encourages oxidative stress, overwhelming the liver's antioxidant defenses and causing hepatocyte damage. This oxidative stress also triggers an inflammatory reaction, leading to the release of cytokines and immune cell activation, which exacerbates inflammation and liver damage (Ferah Okkay *et al*., 2022). CIS also disrupts the function of mitochondria in the hepatic cells, leading to energy depletion and further hepatocellular injury. The drug can trigger apoptosis through the caspase pathway of cell apoptosis. Additionally, CIS affects bile acid metabolism, leading to cholestasis and worsening liver dysfunction (Elsayed *et al*., 2021). Several studies document CIS's hepatotoxic effects (Alkhalaf *et al*., 2023; Gazwi *et al*., 2024; Farouk *et al*., 2025).

Heart: CIS has been allied with cardiotoxicity, leading to cardiovascular complications. The mechanisms underlying CIS-induced cardiotoxicity involve the generation of ROS and oxidative stress (Elsayed *et al*., 2022). Moreover, the cardiac injury biomarkers including troponin, LDH, and CK-MB were elevated in CIS-induced toxicity (Mahmoud Refaie *et al*., 2023). Additionally, the cardiotoxic effects of CIS were mediated by the activation of the PERK signaling pathway, which triggers a cascade of events involving IF2α phosphorylation and caspase-3 activation, ultimately leading to apoptosis in cardiomyocytes and contributing to the development of cardiotoxicity (Hu *et al*., 2018). Furthermore, CIS-induced mtDNA damage evades repair, disrupting mitochondrial ATP production and leading to cardiomyocyte dysfunction and heart failure (Ma *et al*., 2010).

Bone marrow: Bone marrow, the place of red blood corpuscles, white blood corpuscles, and platelet production, can be harmed by CIS. Reduced blood cell production and an elevated risk of infection, anemia, and bleeding can result from bone marrow suppression. CIS induces toxicity through processes such as cell cycle stoppage, apoptosis, oxidation process, inflammatory reaction, and disruption of stem cell. It directly impairs hematopoietic stem cell function, reducing blood cell production and contributing to hematological toxicity (Salehcheh *et al*., 2022; Lin *et al*., 2024).

Gastrointestinal tract: CIS can negatively impact the gastrointestinal (GI) tract, which is essential for digestion, food absorption, and waste removal. Common GI side effects of CIS therapy include nausea, vomiting, diarrhea, mucositis, and loss of appetite. CIS damages GI epithelial cells, generating reactive intermediates that induce stress and injury. The drug also triggers an inflammatory response, which exacerbates mucositis and leads to cytokine release and immune cell recruitment. This results in ulceration and erosion of the GI mucosal barrier (Huang *et al*., 2022). CIS can also alter GI motility, contributing to delayed gastric emptying and bowel irregularities. Additionally, CIS may cause dysbiosis and further gastrointestinal damage by upsetting the gut microbiota (Cabezos *et al*., 2010).

Nervous system: CIS can cause nervous system toxicity, particularly in the peripheral nervous system, by disrupting neurotransmitter systems and impairing neuronal signaling. This may lead to altered neuronal excitability, aberrant nerve conduction, and impaired neural communication (Wang *et al*., 2022). Inflammation caused by CIS activates glial cells and microglia, further contributing to neuronal damage and neuroinflammation. CIS-induced neurotoxicity involves mechanisms like microtubule instability, axonal degeneration, and ion channel dysregulation, which lead to neurotoxic effects (Khalil *et al*., 2023).

Lungs: Although CIS does not primarily target the lungs, some people may get pulmonary damage. CIS may impair lung function by harming the alveolar and airway epithelial cells. In severe cases, this damage can result in pulmonary fibrosis, characterized by fibrotic tissue accumulation and scarring, reducing lung capacity. By damaging endothelial cells, CIS poisoning can also disrupt the blood vessels of the lung, disrupting normal vasculature and reducing oxygenation and blood flow (Soultati *et al*., 2012; Han *et al*., 2021; Mokhtari *et al*., 2023).

Reproductive system: CIS can negatively impact the reproductive system in both men and women. In males, it can cause testicular dysfunction, reducing sperm production and impairing sperm motility, sometimes resulting in azoospermia. CIS may also interfere with testosterone and reproductive hormone regulation, impairing reproductive function (Alharbi *et al*., 2024). In females, CIS can damage ovarian tissue, reducing ovarian reserve and leading to menstrual irregularities, decreased

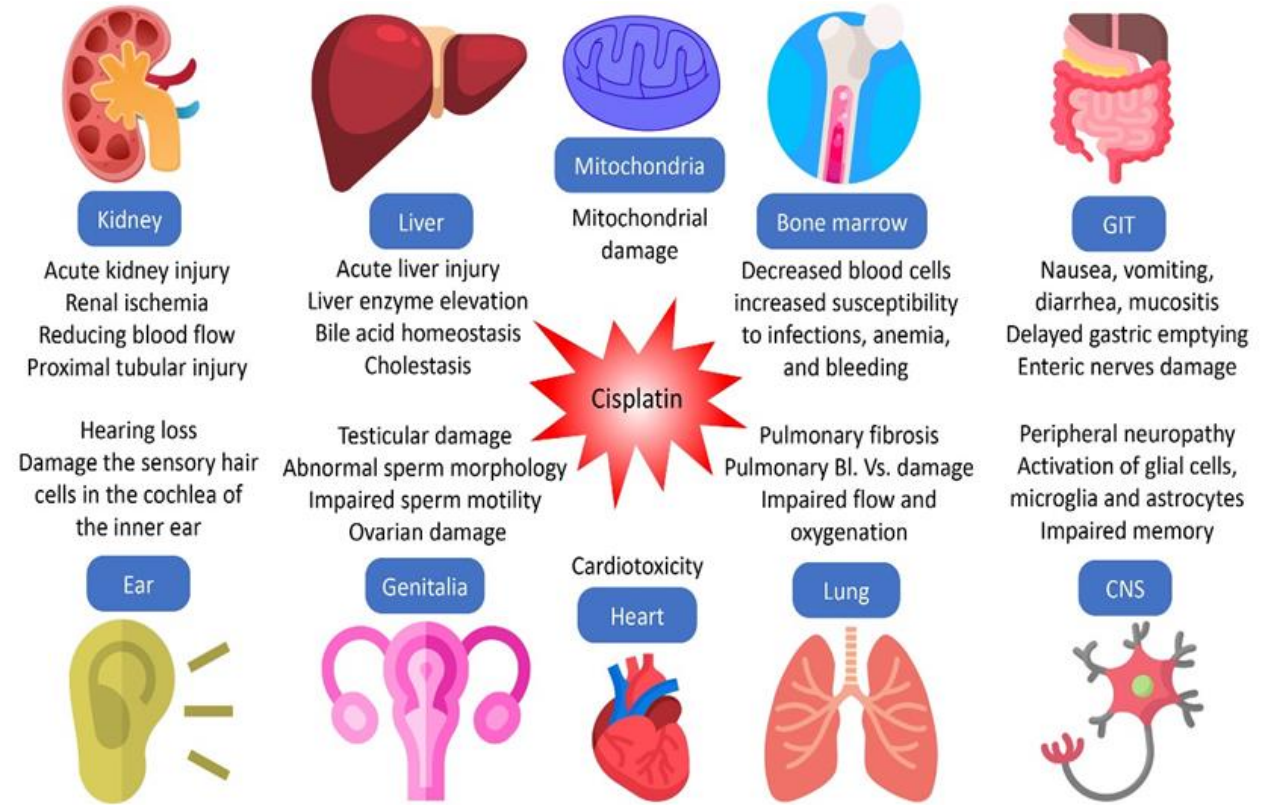

Fig. 1: Overview of the impact of cisplatin-induced toxicity in different organs.

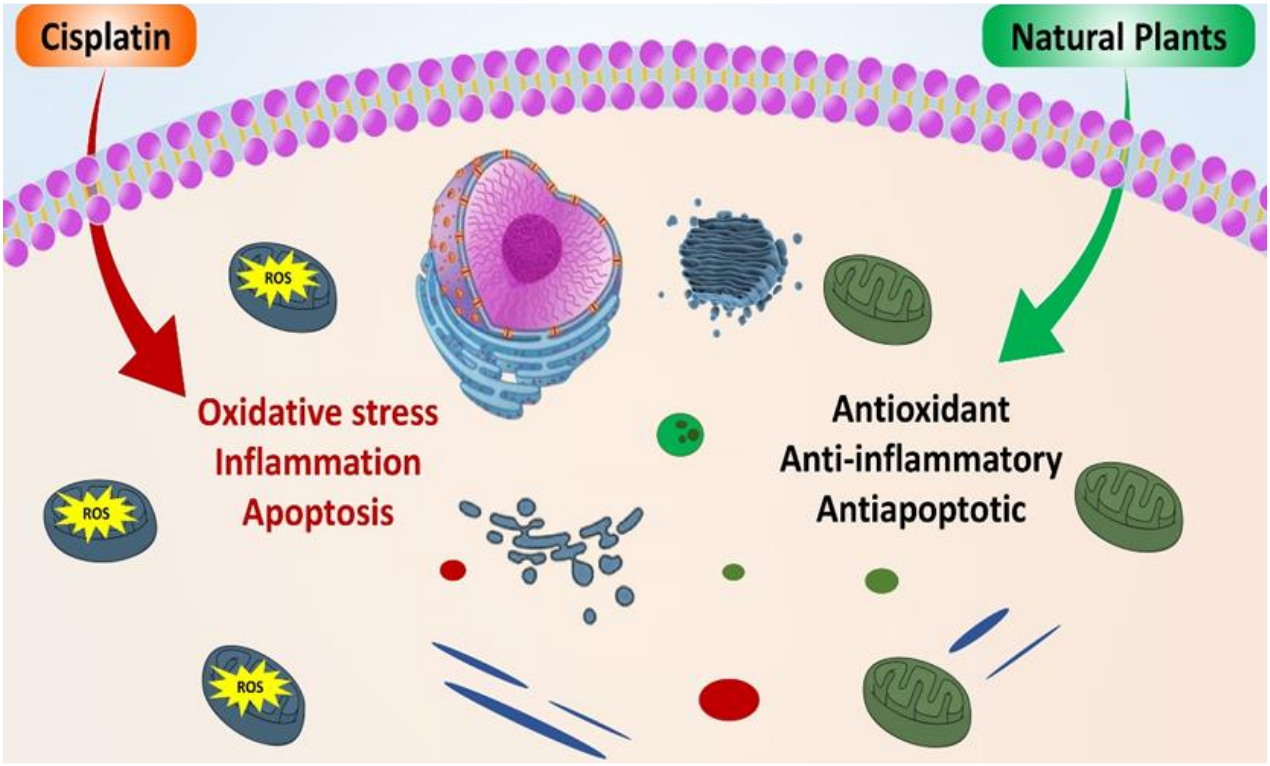

Fig. 2: Overview on the mechanisms of action of cisplatin-induced toxicity and the protective role of natural plants.

fertility, or early ovarian failure (Demir *et al*., 2024). CIS's effects on reproductive hormones can cause hormonal imbalances and disrupt menstruation in women (Ayazoglu Demir *et al*., 2023).

Ears: One of CIS's main negative effects is ototoxicity, which can cause hearing loss and balance issues. Individual susceptibility, treatment length, and CIS dosage all affect how severe this impact is. CIS can damage the cochlea's sensory hair cells, essential for detecting sound vibrations. Treatment can induce the release of ROS in the inner ear, leading to oxidative stress and cellular damage. This triggers an inflammatory response, further exacerbating ototoxicity (Qiao *et al*., 2024).

Table 1: Protective effect of natural plants against cisplatin toxicity.

Plants	Model	Organ	Results	Mechanism of action	References
Artemisia	Cell line	Oral mucosal epithelial cells	Decreasing the mitochondrial damage	Inhibited the NF-κB, decreased cytochrome c and caspase-3, and improved Bcl-2	Chang *et al.* (2015)
	Cell line	kidney epithelial (LLC-PK1) cells	Alleviated nephrotoxicity	Reduced caspase-3, phosphorylated JNK and p38 expression	Park *et al.* (2015)
	C57BL/6J mice	Kidney	Improved acute kidney damage	Decreasing oxidative stress and inflammation Upregulated Nrf-2 and HO-1 and downregulated RAGE and iNOS	Zhang *et al.* (2024)
Cinnamon	Sprague–Dawley rats	Spleen	Ameliorate the induced splenotoxicity	Antioxidant (CAT, MDA) and anti-inflammatory (TNF-α)	Abd El-Raouf *et al.* (2015)
	Cell line	Kidney Vero cells	Suppressed the induced apoptosis	Prevented Bax protein, cytochrome c, caspase-3 activation, DNA fragmentation, and upregulated heme oxygenase (HO)-1	ElKady and Ramadan (2016)
Curcumin	Female Wistar rats	Dorsal root ganglion and sciatic nerves	Improved neuropathy	Improved sciatic motor nerve conduction velocity, improved myelin thickness	Agthong *et al.* (2015)
	Male Wister rats	Brain (hippocampus) Behavior	Improved learning and memory	Antioxidant (MDA, SOD), improved cholinergic function (AChE)	Oz *et al.* (2015)
	Female Sprague–Dawley rats	Kidney	Ameliorated nephrotoxicity	Decreased inflammatory reactions (IL-6, IL-8, IL-10, TNF-α)	Kumar *et al.* (2017)
	Male Wister rats	Renal cortex mitochondria	Alleviated acute kidney injury	Improved mitochondrial function and SIRT3 level	Ortega-Domínguez *et al.* (2017)
	Male Sprague–Dawley rats	Kidney	Inhibited kidney damage	Prevented oxidation (MDA, GSH), reduced inflammatory reactions (TNF-α, NF-κB, IL-10), reduced apoptosis (Bax, Bcl-2)	Soetikno *et al.* (2019)
	Male C57BL/6 mice	Kidney	Ameliorated acute kidney damage	Downregulated miR-181a and upregulated PTEN	Huang *et al.* (2020)
	Adult male C57BL/6j black mice	Optic neuron	Inhibited optic nerve damage	Suppressed mitochondrial ROS production via regulation of TRPM2 signaling pathways	Özkaya and Nazıroğlu (2020)
	Male Wistar rats	Heart	Alleviated cardiotoxicity	Antioxidant (MDA, GSH, NO), anti-inflammatory (TNF-α), enhanced cholinergic function, restored Na+, K+-ATPase activity	Khadrawy *et al.* (2021)
	Male C57BL/6 mice	Stomach (gastric mucosa)	Alleviated inflammatory reactions and apoptosis of gastric mucosa	Reduced the activity of MAPKs and NF-κB signaling pathways	Gao *et al.* (2022)
	Female Wistar rats	Sciatic nerves	Alleviated neuropathy	Antioxidant (GSH/GSSG ratio)	Kobutree *et al.* (2023)
Garlic	Male Sprague–Dawley rats	Kidney	Attenuated nephrotoxicity	Anti-apoptotic, anti-oxidant, and anti-inflammatory properties (reduced activity of NF-κB)	Zhu *et al.* (2017)
	Sprague-Dawley rats	Kidney	Alleviated renal injury	Antioxidant effect, suppressed inflammatory cytokine (NF-κB), and inhibited apoptosis (p53/Puma signaling pathway)	Elkhoely and Kamel (2018)
	Male Wistar rats	Liver and kidney	Improved hepato-renal damage	Antioxidants (SOD, CAT, GSH, NO, and MDA) and preventing renal inflammation (IL-6)	Abdel-Daim *et al.* (2020)
Ginger	Male albino rats	Kidney	Alleviated renal injury	Decreased urea and creatinine levels and Bax proapoptotic protein	Ali *et al.* (2015)
	Male albino rats	Postrema and ileum	Prevent emesis and pica	Inhibited central or peripheral elevation of DA by inhibiting D2R, TH and accelerating DAT.	Qian *et al.* (2016)
	Female Wistar rats	Ovary, uterus	Ameliorated the ovarian and uterine tissue damage	Inhibiting oxidation through elevation of SOD, CAT, GPx, and GSH, and reducing of MDA Alleviating inflammatory reactions through reducing of TNF-α, NF-κB, IL-1β, IL-6, as well as iNOS and COX-2	Kaygusuzoglu *et al.* (2018)
	Male albino rats	Heart	Ameliorated cardiotoxicity	Anti-apoptotic, anti-oxidant, and anti-inflammatory effects (downregulated P53 and TNF-α immune expressions)	El-Hawwary and Omar (2019)
	Female Wistar rats	Kidney	Attenuated nephrotoxicity	Antioxidant (CAT, SOD, GPx, GSH), antiapoptotic (8-OHdG, p53, caspase-3, bax, Bcl-2), anti-inflammatory (through reducing NF-κB, TNF-α, IL-1β, IL-6, IL-33, iNOS, and COX-2)	Kandemir *et al.* (2019)
	Adult male Sprague Dawley rats	Medulla oblongata and ileum	Inhibited pica and emesis	Antiemetic effect via regulation of TPH/MAO-A/SERT/5-HT/5-HT3 receptor	Cheng *et al.* (2020)
	Male albino rats	Testis	Alleviated testicular toxicity	Antioxidant (MDA, GSH, NO), anti-inflammatory (iNOS, NF-κB)	Famurewa *et al.* (2020)
	Male C57BL/6N mice	Kidney	Alleviated kidney dysfunction and tubular damage	Suppressed oxidative stress, tubular cell death, and inflammation	Gwon *et al.* (2021)
	Adult male Sprague	Nodose ganglia of vagus nerve	Alleviated anorexia	Downregulated 5-HT receptors, 5-HT3A and 4	Kim *et al.* (2023)

	Dawley rats				
Ginseng	Male ICR mice	Kidney	Alleviated nephrotoxicity	Suppressed ROS generation through decreased activity of NF-κB and MAPK	Ma *et al*. (2017)
	Wistar rats	Hippocampus	Improved cognitive decline and neuronal loss	Reduced oxidative stress and neuroinflammation and recovered cholinergic neuron functions	Chen *et al.*(2019)
	Male Sprague Dawley rats	Behavior	Reduced neuropathic pain	Spinal 5-HT7 receptors contributed to antiallodynic properties of Korean ginseng	Kim *et al.* (2020)
Lycopene	Female albino Wistar rats	Ovary	Alleviated ovarian toxicity	Antioxidant (MDA, GSH)	Kulhan *et al.* (2019)
	Male Wistar rats	Lung	Ameliorated lung damage	Antioxidant (MDA, PCC), anti-inflammatory (MPO, NO, Citrulline, Arginase), antiapoptotic (Caspase-3, Alkaline DNase, Acid DNase)	Rančić *et al.* (2021)
	Male Wistar rats	Heart	Ameliorated cardiotoxicity and apoptosis	Improved cardiac biomarkers (LDH, CK, CK-MB), antioxidant (MDA, GSH, SOD, CAT)	Elsayed *et al.* (2022)
Moringa	Male albino rats	Kidney	Ameliorated nephrotoxicity	Antioxidant (MDA, NO, SOD), anti-inflammatory (TNF-α, IL-6)	Hussein *et al.* (2024)
N. Sativa	Male albino rats	Kidney	Improved nephrotoxicity	Improved renal functions (urea, creatinine), improved urine glucose concentration	Hosseinian *et al.* (2016)
	Male Wistar rats	Liver	Alleviated hepatotoxicity	Improved energy metabolism, antioxidant effect	Farooqui *et al.* 2016
	Male Wistar rats	Intestine	Improved gastrointestinal dysfunction	Antioxidant effect	Shahid *et al.* 2017
	Male Wistar rats	Intestine (duodenum)	Ameliorated intestinal toxicity	Antioxidant effect, improved carbohydrate metabolism	Shahid *et al.* (2018)
	BALB/c mice	Cultured DRGs neurons	Inhibited neurotoxicity	Enhanced the capability to extend neurites and neuronal cell viability	Üstün *et al.* (2018)
	Male Wistar rats	Oral mucosal tissues	Prevented oral mucositis	Anti-inflammatory, antioxidant	Eğilmez *et al.* (2020)
	Male Wistar rats	Auditory brain stem response	Improved cochlear function	Improved auditory brainstem response measurements and histopathology of cochlea	Kökten *et al.* (2020)
	Male Wistar rats	Brain (hippocampus and cortex)	Improved memory impairment	Antioxidant (MDA, SOD)	Mahmoud Janloo *et al.* (2024)

Brief overview of some natural plants effective against CIS toxicity: An overview of nine herbal plants, along with their mechanisms of action that have been shown to mitigate CIS toxicity in various organs across different animal species was illustrated in Table 1.

Artemisia: Around the world, traditional herbal medicine uses a variety of *Artemisia* species. The most well-known species are *Artemisia absinthium, Artemisia abrotanum, Artemisia vulgaris,* and *Artemisia dracunculus*. However, the discovery of artemisinin, a sesquiterpenoid lactone that is found in *Artemisia annua* and is effective in treating malaria, in 2015 marked a significant advancement in the search for *Artemisia* from the standpoint of scientific research (Ekiert *et al*., 2022). Moreover, the most important phytochemical composition of the *Artemisia species* is the sesquiterpenoid lactone, artemisinin, found in *A. annua, A. abrotanum,* and *A. vulgaris*. Other sesquiterpenoid lactones, artemisinic acid, and artannuin B are detected in *Artemisia annua*. Furthermore, absinthin, anabsinthin, anabsin, artabsin, and absintholide are compounds that present in high levels in different species of *Artemisia* (Cala *et al*., 2015). Flavonoids such as artemetin, quercetin, kaempferol, apigenin, and luteolin are present in *Artemisia species.* In addition, other groups of metabolites were reported as coumarin and phenolic acids (Jahani *et al*., 2019).

Newer data indicated that the novel drug, Artesunate-Nanoliposome-TPP, derivative from artemisinin isolated from *Artemisia annua L.* improved CIS-induced acute kidney damage in C57BL/6J mice model. The study suggested the mechanism by which Artesunate-Nanoliposome-TPP ameliorates CIS-induced nephrotoxicity, and it is mainly attributed to its antioxidative and anti-inflammatory properties via upregulation of Nrf2 and HO-1 and downregulation of RAGE and iNOS (Zhang *et al*., 2024). Chang and his team in an earlier study suggested that the ethanol extract of *Artemisia asiatica* alleviated CIS-induced injury of mitochondria allied with the activity of Bcl-2 by hindering the NF-κB nuclear translocation in the Human HaCaT cell model (Chang *et al*., 2015).

Cinnamon: Cinnamon is herbal plant belonging to the family of Lauracease, known scientifically as *Cinnamomum cassia*, and an inhabitant worldwide. It is a favorite spice with a special flavor used in traditional medicine. Cinnamaldehyde and eugenol are the main active ingredients in cinnamon, while there are also trace amounts of coumarin, cinnamonyl alcohol, hydroxyl cinnamonaldehyde, cinnamic acid, and cinnamonyl acetate. Antibacterial, antidiabetic, and anticancer properties of cinnamon have been reported in different studies (Khedkar and Ahmad Khan, 2023). It has been shown that cinnamon's antioxidant and anti-inflammatory properties contribute to its protective properties against CIS-induced spleen toxicity, as many factors enhanced the activity of CAT and reduced MDA and TNF-α levels in Sprague–Dawley rats' model (Abd El-Raouf *et al*., 2015). Moreover, the cytoprotective effect of cinnamon against CIS toxicity was illustrated in the Kidney Vero cells study by ElKady and Ramadan. In their study, the authors reported that cinnamon prevented Bax protein, cytochrome c, caspase-3 activation, DNA fragmentation, and upregulated heme oxygenase $(HO)^{-1}$ (ElKady and Ramadan, 2016).

Curcumin: Curcumin (diferuloylmethane) is a powerful bioactive compound found in *Curcuma longa*; a tropical herb grown in the tropics that has been used in traditional medicine for centuries. Additionally, curcumin is the major constituent of turmeric, which is a common spice, especially in Asia. There have been several studies reported that curcumin has antioxidant, anti-inflammatory, lipid-lowering anti-tumor, anti-arthritic, immunoregulatory, hepatoprotective, anti-ischemic, cognitively enhancing, antipruritic, pulmonary protective, antidepressant, and analgesic effects (Hosseini-Zare *et al.*, 2021). Curcumin has been known to mitigate CIS-induced toxicity in many organs. In particular, it alleviated CIS-nephrotoxicity by the antioxidant (MDA), anti-inflammatory (TNF-α, IL-1b, IL-6, IL-10), and antiapoptotic (p53, Fas, Fas-L) in adult male Wistar rat model. Another experiment was conducted on the same animal model where the curcumin enhanced the mitochondrial function and SIRT3 level in the renal cortex (Ortega-Domínguez *et al*., 2017). The authors examined how cinnamon's potent antioxidant, anti-inflammatory, and antiapoptotic qualities could prevent acute kidney damage brought on by CIS in the models of C57BL/6 male mice and Sprague-Dawley male rat and the downregulation of miR-181a and upregulation of PTEN (Huang *et al*., 2020), respectively. Moreover, two studies were performed by Kumar and his team on the female Sprague–Dawley rat model in 2017. They concluded that curcumin detoxified CIS-renal injury by combating inflammation and enhancing of kidney function. Administration of curcumin prior to CIS-treatment significantly enhanced the anti-inflammatory markers (TNF-α, IL-1β, IL-6, IL-8, and IL-10) and reduced BUN and creatinine level (Kumar *et al*., 2017). Tan and his colleagues proved the anti-inflammatory effect of curcumin in mouse macrophage cell line RAW264.7 of male C57BL/6 mice. They found that curcumin restored anti-inflammatory markers including IL-1β, IL-6, TNF-α, and MCP-1 (Tan *et al*., 2019). The efficacy of curcumin against CIS toxicity and found that the curcumin reduced the adverse effect of CIS on the liver and brain by restoring the mitochondrial lipid peroxidation and protein carbonyl levels (Waseem and Parvez, 2013).

Moreover, curcumin ameliorated the neuropathy effect of CIS by improving the sciatic motor nerve conduction velocity and myelin thickness. Based on these results, Özkaya and Nazıroğlu (2020) conducted a study in a model of optic nerve damage of adult male C57BL/6j black mice obtained with CIS (4 mg/kg body weight) combined with curcumin (30 mg/kg body weight). They concluded that curcumin was able to mitigate optic nerve damage by suppressing the mitochondrial ROS production and regulation of TRPM2 signaling pathways. These results were confirmed by the study of Kobutree and his team on the sciatic nerve of the female Wistar rat model.

One of the most crucial adverse effects of CIS toxicity is the inflammation of gastric mucosa. Notably, curcumin improved the gastric empty by modulation of ACh transmission and repairing the structure and function of interstitial cells of Cajal (Li et al., 2020) and alleviating the inflammatory reactions by regulating the expression of the inflammatory cytokines (NF-κB and MAPKs signaling pathway) (Gao *et al*., 2022). Noteworthy, CIS-induced cardiotoxicity by a single dose (12 mg/kg i.p.) was protected by nanoparticles of curcumin at a 14 days dosage of 50 mg/kg via the antioxidant (MDA, GSH, NO), anti-inflammatory (TNF-α) effects, enhancing the cholinergic function and restoring Na+, K+-ATPase activity (Khadrawy *et al*., 2021).

Garlic: Garlic (*Allium sativum L.*), a highly aromatic herbaceous annual spice belonging to the Amaryllidaceae Family, has been utilized in traditional medication for thousands of years and is one of the most significant and oldest plants on earth. It contains biologically active sulfur-containing compounds, including allicin, alliin, and allyl mercaptan. Interestingly, interference between garlic constituents' administration and the CIS-nephrotoxicity could exist. Diallyl sulfide and S-Allylmercaptocysteine attenuated the CIS-induced renal damage by preventing the oxidative stress (elevation of GSH and SOD, and reducing of MDA), hindering the inflammatory reaction (NF-κB), and alleviating the cell apoptosis (p53/Puma) properties (Elkhoely and Kamel, 2018).

Furthermore, the ameliorated effect of garlic extract on the kidneys of pregnant female Wistar rats and their offspring. They concluded that the garlic extract ameliorated the CIS-induced renal damage in pregnant rats and their offspring by restoring the activity of GPx, CAT, SOD, caspase 3, and the level of MDA in addition to the improved histopathological renal lesions (Elbeltagy *et al*., (2022). Moreover, garlic extract was found to improve the enzymatic and enzymatic antioxidants (SOD, CAT, GSH, NO, and MDA) and anti-inflammatory (IL-6) in the hepatorenal tissues of rats (Abdel-Daim *et al*., 2020).

Ginger: Ginger (*Zingiber officinale*) has been extensively used as a spice and is considered as one of the oldest authenticated and most important herbs that have been used from olden times as traditional medicine to treat gastric problems, fevers, sore throats, coughs, and so on. The chemical composition of ginger is very rich, containing phenolics and terpenoids. It contains phenolic ingredients such as gingerol, zingerone, shogaol, and paradol. In addition, lipids, carbohydrates, organic acids, fiber, and other nutrients are present in the chemical composition (Elshafae *et al*., 2023). Notably, several reports demonstrated the nephron-protective effect of ginger against CIS toxicity. Ali *et al*. (2015) observed the decreased urea and creatinine levels and Bax proapoptotic protein by every other day treatment of ginger extract for 4 weeks (120 mg/kg in male albino rats) (Ali *et al*., 2015). A more detailed study was performed by Kandemir *et al*., (2019) who evaluated the impact of a 7-days (once a day) of two doses of zingerone (25 and 50 mg/kg b. wt.) against CIS-induced nephrotoxicity (7 mg/kg b. wt. i.p. at the 1st day) in female Wistar rat model. They noticed the ameliorating effect of zingerone (recovery of the renal histological characteristics). In addition, zingerone restored the antioxidant cascade (CAT, SOD, GPx, GSH), antiapoptotic markers (8-OHdG, p53, caspase-3, bax, Bcl-2), and anti-inflammatory markers (IL-1β, IL-6, IL-33, NF-κB, iNOS, TNF-α, COX-2) (Kandemir *et al*., 2019). A recent study, in which the mechanisms of 6-shogaol protected effect on CIS-induced nephrotoxicity has been conducted by Gwon et al., in male C57BL/6N mice. The

authors reported that 6-shogaol suppressed oxidative stress, tubular cell death, and renal inflammation (Gwon *et al*., 2021).

An experiment was performed by El-Hawwary and Omar for discussing the protective role of the 12-day dosage (once a day) of ginger extract (500mg/kg) against CIS-induced cardiotoxicity (2mg/kg/day i.p. for 1 week) in male albino rat model. The authors found that ginger extract ameliorated the cardiac damage (improved the cardiac tissue histology and structure) by Anti-apoptotic, anti-oxidant and anti-inflammatory effects (downregulated P53 and TNF-α immune expressions) (El-Hawwary and Omar, 2019). It is obvious that zingerone ameliorated the CIS-induced ovarian and uterine inflammation as it was associated with the powerful detoxifying mechanisms by removing the oxidative stress through increasing SOD, CAT, GPx, and GSH, and reducing MDA, and hindering the inflammatory reactions through suppression of IL-1β, NF-κB, TNF-α, IL-6, COX-2, and iNOS (Kaygusuzoglu *et al*., 2018). On the other hand, the testicular damage induced by CIS (10 mg/kg b. wt. on day 2 only) was improved by oral ginger juice (5 ml/kg b. wt. from first day to the fifth day) via the antioxidant (MDA, GSH, NO), and anti-inflammatory (iNOS, NF-κB) mechanisms (Famurewa *et al*., 2020).

Moreover, gingerol revealed effective dose-dependent inhibition on the elevation of dopamine 2 receptor, dopamine transporter and tyrosine hydroxylase expression levels in the CIS vomiting model of rats (Qian et al., 2016). Furthermore, the regulation of the TPH/MAO-A/SERT/5-HT/5-HT3 receptor by gingerol has been linked to the antiemetic effect of CIS, as reported by Cheng *et al*. (2020). Based on these consequences, Kim *et al*. (2023) demonstrated that ginger alleviated anorexia via downregulating 5-HT receptors, 5-HT3A, and 4.

Ginseng: Ginseng has been utilized as a tonic in the oriental medication; it is widely recognized as a dietary supplement and energy enhancer. A significant part of ginseng extract is ginseng saponin, and ginsenoside is a particular type of ginseng saponin glycoside. Over 40 ginsenosides have been identified from various ginseng species. There are various positive benefits of ginsenosides (Park *et al*., 2021). The sickness behaviors induced by CIS were improved by ginseng extract via improved malaise, body weight, hypothermia, hyperalgesia, and running time (Lobina *et al*., 2014). In addition, it reduces neuropathic pain via the antiallodynic effect of Korean ginseng (Kim *et al*., 2020). Moreover, Chen *et al*., (2019) studied the outcome of coadministration of ginsenoside (2 mg/kg/d in drinking water) and CIS (5mg/kg/wk, i.p.) on the hippocampus. They recorded that ginsenoside improved cognitive decline and neuronal loss by the action of reducing oxidative stress (SOD, GPx, MDA, ROS) and neuroinflammation (TNF-α, IL-1β, IL-10), and recovering the cholinergic neuron functions (choline acetyltransferase, acetylcholinesterase, acetylcholine).

Furthermore, the haematological and histopathological findings in the tissues of the stomach and small intestine of male rats treated with CIS were improved by Korean ginseng root extract via improving feed intake, alleviating pica, and resisting emesis (Raghavendran *et al*., 2011). According to Ma *et al*. (2017), ginseng hindered the deleterious impact of ROS by lessening the expression of NF-κB and MAPK and thus alleviated CIS-induced nephrotoxicity in male ICR mice.

Lycopene: Lycopene (a non-provitamin A carotenoid) is the most important component present in various plants as tomatoes and watermelons. The antioxidant efficacy of lycopene exceeded that of vitamin E and glutathione by more than 100 and 125 times, respectively (Shafe *et al*., 2021). Herein, the protective effect of lycopene and Ginkgo biloba on CIS-dependent ototoxicity in a rat model was conducted by Ciçek *et al*. (2014). The authors found that lycopene inhibited ototoxicity at low frequencies via the antioxidant effect. The study on the lungs of rats conducted by Rančić *et al*. (2021) proved the ameliorated effect of lycopene against CIS-induced lung damage via the antioxidant (MDA, PCC), anti-inflammatory (MPO, NO, Citrulline, Arginase), and antiapoptotic (Caspase-3, Alkaline DNase, Acid DNase) effects. Moreover, the protective effect of lycopene against toxicities of CIS on male and female genital systems were illustrated in various studies. They recorded the alleviation of ovarian and testicular damage by hindering the oxidative stress (MDA, GSH, SOD, CAT) and the antiapoptotic effect (Caspase-3) (Cevik *et al*., 2012; Elsayed *et al*., 2022). Interestingly, Erman *et al*. (2014) showed that lycopene inhibited the CIS-induced renal inflammation by anti-inflammatory effect (NF-κB) and upregulation of OAT1 and 3 and OCT1 and 2.

***Moringa oleifera L.*:** *Moringa oleifera L*. (Moringaceae) is a common tree in Asia and Africa's tropics and subtropics. The chemical composition contains several compounds such as flavonoid pigments (kaempferol, rhamnetin, isoquercitrin, and kaempferitrin) which are found in *Moringa oleifera* leaves. These leaves are also abundant in beta-sitosterol, glycerol-1-(9-octadecanoate), 3-O-(6'- O-oleoyl-beta-D-glucopyranosyl), beta-sitosterol, and betasitosterol-3-O-beta-D-glucopyranoside, in addition to a group of glycoside chemicals, glucosinolates, and isothiocyanates (Liu *et al*., 2022). The recorded nephroprotected effect of *Moringa oleifera* extract against CIS-induced toxicity was illustrated in the study of Hussein *et al*., (2024) as a result of the antioxidant (MDA, NO, SOD) and anti-inflammatory (TNF-α, IL-6) effect. Moreover, *Moringa oleifera* possesses an immunomodulatory role in alleviating aflatoxicosis in Nile tilapia (Abdelhiee *et al*., 2021).

Nigella sativa: *Nigella sativa*, a member of the Ranunculaceae family, is an annual plant that is widely spread, especially in North Africa, the Middle East, Europe, and Asia. It is often referred to as "black cumin" or "black seeds". For thousands of years, Arab, Indian, and European nations have utilized black cumin for both culinary and therapeutic uses. According to a widely held Muslim belief, "Habba sawda", as it is known in Arabic, is a cure-all for all illnesses except for preventing death (AbdulAzeez *et al*., 2020). *N. sativa's* chemical composition includes proteins, alkaloids, saponins, fixed

oils, and essential oils. Thymoquinone, dithymoquinone, thymohydroquinone, and thymol are the principal active ingredients of essential oils (Dalli *et al*., 2021). According to Abdo *et al*., (2021), thymoquinone hindered the oxidative stress in pulmonary tissue induced by malathion inhalation. Herein, the neuroprotective effect of thymoquinone against CIS-induced toxicity in cultured DRGs neurons was recorded by enhancing the capability to extend neurites and neuronal cell viability (Üstün *et al*., 2018). Recently, and based on these results, Mahmoud Janloo *et al*. (2024) reported the improvement of memory impairment by thymoquinone on the hippocampus and cortex of a CIS-treated male rat model. They owed these findings to the antioxidant characteristics of thymoquinone (MDA, thiol, SOD). Moreover, thymoquinone improved the auditory brainstem response measurements and histopathology of the cochlea in the study of CIS-ototoxicity (Kökten *et al*., 2020). Additionally, the hepatoprotective effect of *N. sativa* oil against Cis-induced toxicity was discussed by its antioxidant effect and improvement of the energy metabolism in addition to restoring the liver histopathology structure (Farooqui *et al*., 2016). The principal dose-limiting deleterious effect of CIS is nephrotoxicity. In the experiment of Hosseinian *et al*. (2016), the authors concluded that *N. sativa* extract (200 mg/kg b.wt.) was able to improve renal functions (urea, creatinine), and urine glucose concentration. Based on these findings, *N. sativa* extract and thymoquinone alleviated CIS-nephropathy by different mechanisms including the antioxidant effect (MDA, SH, GSH, SOD, CAT, GPx, TR, GR, GST), and improved carbohydrate enzymes (HK, LDH, MDH, G6Pase, FBPase, G6PDH, ME) (Farooqui *et al*., 2017).

Moreover, alleviation of CIS-induce renal toxicity by all parts of *N. sativa* (powder, oils, and extract) was performed by reduced serum levels of urea, creatinine, and potassium, and augmented Na, Na/K, vitamin D, nutritional markers, and antioxidant effect (CAT, SOD, GPx, MDA) (Alsuhaibani, 2018). A comparative study between *N. sativa* (200 mg/kg b.wt.) and vitamin E (100 mg/kg) was conducted by Busari *et al*. (2018). The authors demonstrated that *N. sativa* significantly reduced CIS-induced nephrotoxicity via decreasing urea, creatinine, Na, and MDA levels in addition to increasing the activity of CAT, and SOD.

Conclusions: This review has highlighted the promising protective effects of some natural plants, including Artemisia, Cinnamon, Curcumin, Ginger, Garlic, Ginseng, Lycopene, Moringa, and *N. sativa* against CIS-induced toxicity. The evidence existing suggests that these plants, through their various bioactive compounds, offer the potential for mitigating the severe side effects associated with CIS chemotherapy. While the mechanisms of action vary, many converge on reducing oxidative stress, inflammation, and apoptosis, key pathways implicated in CIS's damaging effects on various organs. While research has demonstrated the protective effects of medicinal plants against CIS toxicity, several critical areas remain unexplored. These include conducting clinical trials in humans, determining optimal dosages, elucidating the mechanisms of action, and examining potential interactions with chemotherapy. To address these gaps, future studies should prioritize clinical validation, investigate the pharmacological activity of plant-derived compounds, assess their synergy with chemotherapy, and explore strategies to enhance CIS efficacy while minimizing its toxic effects. Ultimately, the goal is to establish evidence-based approaches to mitigate CIS toxicity and improve the quality of life for cancer patients.

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