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CURRENT PERSPECTIVES

The Therapeutic Potential of Antioxidants in Chemotherapy-Induced Peripheral Neuropathy: Evidence from Preclinical and Clinical Studies

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Abstract

As cancer therapies advance and patient survival improves, there has been growing concern about the long-term adverse effects that patients may experience following treatment, and concerns have been raised about such persistent, progressive, and often irreversible adverse effects. Chemotherapy is a potentially life-extending treatment, and chemotherapy-induced peripheral neuropathy (CIPN) is one of its most common long-term toxicities. At present, strategies for the prevention and treatment of CIPN are still an open problem faced by medicine, and there has been a large amount of previous evidence that oxidative damage is involved in the process of CIPN. In this review, we focus on the lines of defense involving antioxidants that exert the effect of inhibiting CIPN. We also provide an update on the targets and clinical prospects of different antioxidants (melatonin, N-acetylcysteine, vitamins, α-lipoic acid, mineral elements, phytochemicals, nutritional antioxidants, cytoprotectants and synthetic compounds) in the treatment of CIPN with the help of preclinical and clinical studies, emphasizing the great potential of antioxidants as adjuvant strategies to mitigate CIPN.

Keywords Antioxidants · CIPN · Reactive oxygen species · Antinociceptive · Neurotoxicity · Line of defense

Introduction

As advances in cancer therapies have improved patient survival, there are growing concerns about the long-term side effects of cancer therapy, and chemotherapy-induced peripheral neuropathy (CIPN) can persist for months or even years after the completion of treatment [1]. CIPN occurs in up to 80% of cancer patients receiving cytotoxic chemotherapeutic agents, in which the class of antineoplastic agents, therapeutic dose and duration affect the severity and pathophysiology of the disease [2, 3]. Common symptoms of CIPN include persistent stinging, burning, and loss of sensation in the absence of noxious stimuli, usually manifested as a "stocking and glove" distribution [4]. The quality of life of patients with CIPN can be greatly impaired, sometimes even leading to the delay or suspension of cancer treatment [5]. Therefore, it is suggested to researchers and clinicians that seeking the means to prevent or treat CIPN may become the key to effectively controlling cancer and improving the quality of life of cancer survivors.

There are two main symptoms of peripheral neuropathy in patients with CIPN: one is a gain of function manifestation (characterized by burning pain, pinprick sensation, and sensitivity to cold and touch), and the other is a loss of function manifestation (characterized by loss of proprioception, diminished vibration and pinprick sensation, accompanied by numbness) [6–8]. When assessing the presence and extent of neuropathy in cancer patients, the type of administration, cumulative dose, clinical symptoms and time course of CIPN need to be analyzed.

The first step is to determine whether the patient has received chemotherapy with neurotoxic chemotherapy. Taxanes (e.g., paclitaxel, docetaxel), platinum agents (e.g., oxaliplatin, cisplatin, carboplatin), vinca alkaloids (e.g., vincristine), thalidomide, epothilone (e.g., ixabepilone), and bortezomib have high potential to induce CIPN. However, for some other agents, such as cyclophosphamide or

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methotrexate, the likelihood of inducing CINP is low, and only a single case has been reported in the literature [9]. Second, the route of administration of chemotherapeutics is also important for neuropathy. Intrathecal methotrexate increases the occurrence of neurotoxicity compared with other routes, whereas subcutaneous bortezomib decreases CIPN [10, 11]. Next, the dose of chemotherapy patients received was also associated with the development of CIPN, mostly in a dose-dependent manner, with symptoms typically starting in the first 2 months of treatment and worsening as chemotherapy progressed. However, there are other drug-specific features, such as acute neurotoxic effects of paclitaxel and oxaliplatin or persistence of neuropathy after discontinuation of cisplatin. Affected sites of chemotherapy toxicity in the peripheral nervous system are shown in Fig. 1.

A 2014 study by the American Society of Clinical Oncology reviewed 48 randomized clinical trials of CIPN, and the committee found that no drug was effective for CIPN prevention [12]. In addition, there are no FDA-approved treatments for chemotherapy-induced neuropathic pain, while currently, only one drug, duloxetine, is recommended to treat existing CIPN with "moderate confidence" based on the Brief Pain Inventory-Short Form [13]. Chemotherapy is a treatment that may prolong the patient's life, so it is exceptionally difficult to discontinue chemotherapeutic agents in antitumor therapy. Moreover, patients may not admit or report their neurotoxic symptoms to their physicians because of concerns about losing an effective way to treat their tumor. Therefore, it has become a research hotspot to minimize adverse reactions such as CIPN while ensuring the efficacy of chemotherapy and thus improving the quality of life of patients.

Oxidative Stress and Damage: A Vital Pathogenic Mechanism of CIPN

It is well established that the production of reactive oxygen species (ROS) by antineoplastic agents induces apoptosis in cancer cells [14]. However, ROS generated during chemotherapy may be associated with events such as cardiotoxicity, nephrotoxicity, and neurotoxicity and may interfere with normal cells and tissues. In addition, studies have shown that structural and functional damage caused by anticancer agents can enhance mitochondrial free radical production [15]. The resulting oxidative stress causes damage to neurons by inducing mitochondrial dysfunction, microtubule damage with demyelination, and apoptosis [16]. Certain functional and structural attributes of the peripheral nervous system (PNS) make it more susceptible to the accumulation of chemotherapeutic agents and some neurotoxins, and mammals are more susceptible to oxidative stress due to their high phospholipid content, abundant mitochondrial axoplasm, and weak cellular antioxidant defenses [17, 18]. Moreover, some antioxidant agents have been tested in animal models for CIPN treatment, ameliorating neurotoxicity by reducing oxidative stress [19].

Research evidence shows a relationship between oxaliplatin-induced neuropathy and oxidative stress. The oxidative stress byproducts after its exposure (such as H_2O_2, hypochlorite, nitroleic acid and other endogenous molecules) can regulate transient receptor potential A1 (TRPA1) [20–22]. Simultaneously, oxaliplatin significantly increases superoxide anion production, followed by high levels of intracellular ROS that may in turn lead to enzyme, lipid and protein damage, which leads to structural changes in peripheral nerves [23, 24]. Apoptotic changes following oxidative stress were also

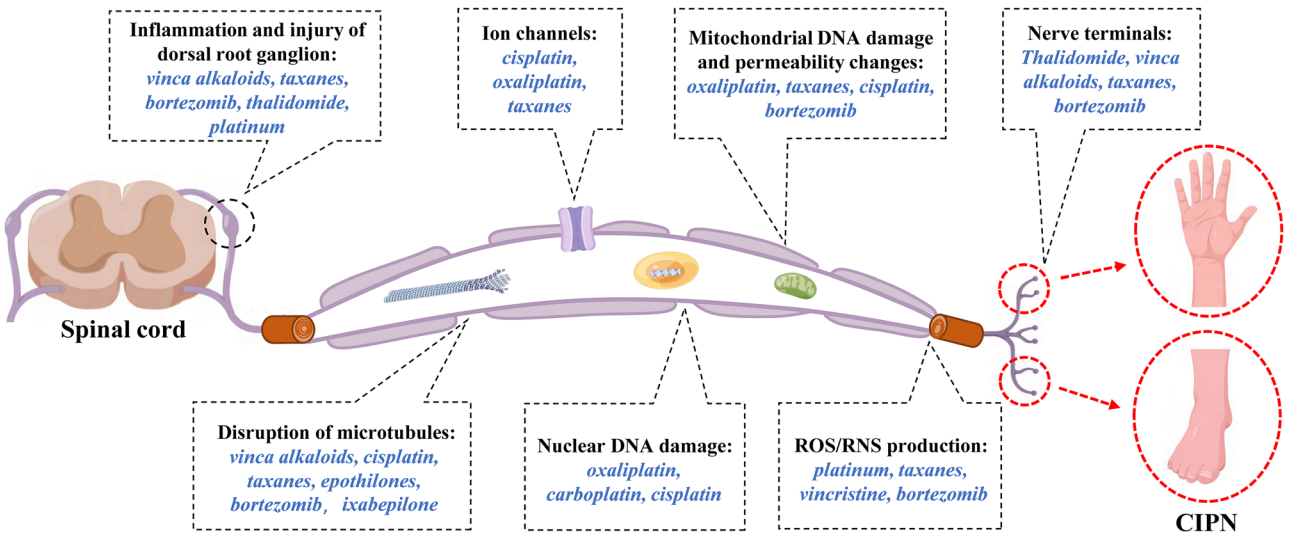

Fig. 1 Chemotherapy toxicity and putative sites of CIPN in the peripheral nervous system

observed in the sciatic nerves of cisplatin-treated mice [25]. However, paclitaxel-induced mechanical hypersensitivity is due to central (spinal) oxidative stress maintaining central sensitization and abnormally processing Ab fiber inputs as nociceptive [26]. Other evidence has shown that MnSOD, CuZnSOD and GPx activities are significantly increased at the peak of paclitaxel-induced painful neuropathy (PIPN), accompanied by an insufficient endogenous antioxidant enzyme response and neuron-derived mitochondrial ROS [27]. Unlike platinum-induced mitochondrial dysfunction, vincristine may alter mitochondrial Ca^{2+} signal transduction [5, 6] and promote signal expression in the process of inducing oxidative damage (including NOX1, NOX2 and iNOS), leading to oxidative stress of sciatic nerve tissue, and antioxidants such as HO-1 and NQO-1 are highly decreased [28]. In addition, bortezomib treatment can also lead to mitochondrial damage, causing mitochondria to produce a large amount of reactive oxygen species (ROS), thereby damaging mitochondrial function and producing cytotoxic effects [29].

Since there is substantial evidence that oxidative damage is involved in the processes of CIPN, it is not surprising that enormous efforts have been made to mitigate the impact of chemotherapy regimens on the quality of life of patients by using antioxidants as potential protective interventions during chemotherapy-based treatment. This article aims to provide an updated review of the therapeutic targets and clinical prospects of different antioxidants (melatonin, N-acetylcysteine, vitamins, α-lipoic acid, mineral elements, phytochemicals, nutritional antioxidants, cytoprotectants and synthetic compounds) in CIPN with reference to preclinical and clinical studies.

Antioxidants in the Treatment of CIPN: Classification and Lines of Defense

The most comprehensive current definition of antioxidants is described as direct scavenging of free radicals, inhibition of free radical generation or indirect upregulation of antioxidant defenses [30]. The mechanism of antioxidant protection in humans occurs through three lines of defense: (1) preventive antioxidants; (2) radical-scavenging antioxidants and repair; and (3) de novo antioxidants. There is also an adaptive mechanism of antioxidant defense, known as "the fourth line of defense" [31–33].

Antioxidants can be divided into enzymatic and nonenzymatic ROS scavengers according to their biological functions. The first line of defense prevents biomolecular damage by preventing the formation of free radicals and their derivatives, which involves the action of enzymatic antioxidants that catalyze the disproportionation of ROS, including superoxide dismutase (SOD), catalase (CAT), glutathione reductases (GRs), glutathione peroxidases (GPxs) and glutathione-S-transferases (GSTs). In addition, the first line of antioxidant defense is also composed of proteins in plasma and represents nonenzymatic antioxidants that bind multivalent metal ions, participate in redox reactions and produce free radicals; these antioxidants include myoglobin, albumin, metallothionein, ceruloplasmin, lactoferrin, ferritin and transferrin [34]. The second line of defense consists of nonenzymatic antioxidants that act as intermediate defenders to scavenge ROS or reactive nitrogen species (RNS); these mainly include vitamins (vitamins A, C, E and K), melatonin, coenzyme Q10 (CoQ10), uric acid, bilirubin, carotenoids, alpha-lipoic acid (ALA), glutathione (GSH) and its precursor N-acetylcysteine (NAC) [33]. Next, the third line of defense (de novo antioxidants) is mainly responsible for repairing or eliminating biomolecular structural damage caused by free radicals and inducing the regeneration of damaged biomolecules from oxidative damage, including DNA repair enzyme systems, lipases, and proteolytic enzymes that can repair damaged molecules [33, 35]. In addition, "the fourth line of defense" may be activated by the reaction and generation of free radicals, which in turn induces the production and transport of corresponding antioxidant enzymes to the effective site and causes the formation of catalase and superoxide dismutase [32, 35].

Nonenzymatic and enzymatic antioxidants act complementarily to each other in different cellular compartments and against different oxidative species and function synergistically with exogenous antioxidant systems. However, considering that the human body's endogenous antioxidant system is not sufficient, the human body can hardly produce nonenzymatic antioxidants, so it depends on exogenous nonenzymatic antioxidants, such as mineral elements, nutritional antioxidants, phytochemicals, cytoprotectants and synthetic compounds (Table 1) [34, 36]. Given this, based on the above antioxidant classification and defense categories, we selected antioxidants that are more studied in CIPN and have a more significant role in a systematic review to provide a reference for the future application and continued research of antioxidants in CIPN.

Preclinical and Clinical Evidence of CIPN: Major Antioxidants in Lines of Defense

Melatonin

Melatonin, which is synthesized by all kinds of cells, is principally secreted by the pineal gland and is known for maintaining aging, reproductive function, circadian rhythm and antioxidant activity [37]. As the second line of defense, it is considered to be an effective antioxidant that can penetrate cell membranes and concentrate within mitochondria

Table 1 Classification and lines of defense of antioxidants

Lines of defense	Antioxidant sources (Enzymatic/Non-Enzymatic)		Antioxidants
The first line	Endogenous antioxidants (Enzymatic)		Superoxide dismutase (SOD)
			Catalase (CAT)
			Glutathione reductases (GRs)
			Glutathione peroxidases (GPxs)
			Glutathione-S-transferases (GSTs)
	Endogenous antioxidants (Non-Enzymatic)		Myoglobin
			Albumin
			Metallothionein
			Ceruloplasmin
			Lactoferrin
			Ferritin
			Transferrin
The second line	Endogenous antioxidants (Non-Enzymatic)		Melatonin
			Coenzyme Q10
			Uric acid
			Bilirubin
			Glutathione
			N-acetylcysteine
			Vitamin A (retinoic acid)
	Exogenous antioxidants (Non-Enzymatic)	**Vitamins**	Vitamin C (ascorbic acid)
			Vitamin E (tocopherols)
			Vitamin K
		Nutritional	Carotenoids
		Supplements	Alpha-lipoic acid
The third line		**De novo antioxidants**	DNA repair enzyme systems
			Lipases
			Proteolytic enzymes
The fourth line	Reaction and generation of free radicals		Antioxidant enzymes
Other exogenous supplements	Exogenous antioxidants (Non-Enzymatic)	**Mineral elements**	Selenium
			Zinc
			Manganese
			Magnesium
		Phytochemicals	Curcumin
			Hesperidin
		Nutritional antioxidants	Omega-3 fatty acids
			Carnosine
			Polyphenol
			Taurine
		Cytoprotectants	Amifostine
			Calmangafodipir
		Synthetic compounds	7-Chloro-4-(phenylselanyl) quinoline (4-PSQ)
			Donepezil

to modulate mitochondrial function by interacting with mitochondrial MT1 receptors [38, 39], and many of its reaction products and metabolites (e.g., 6-hydroxymelatonin) also have antioxidant activity [40, 41]. As a neurohormone, melatonin has antioxidant effects [42], and it also exerts potential antitumor effects through different properties, with signs of antiproliferative and proapoptotic effects and induction of rapid processing of both caspases (3 and 9)

[43]. Therefore, melatonin is believed to reduce the status of CIPN by limiting the development of mechanical hypersensitivity and altering peripheral nerve function.

Previous preclinical studies showed that in paclitaxel-induced CIPN models, oral melatonin pretreatment significantly reduced paclitaxel-induced mechanical allergic reactions in male and female animals by decreasing paclitaxel-induced 8-isoprostane F2α levels and C-fiber activity-dependent slowing (ADS) in peripheral nerves, and importantly, melatonin cotreatment with breast or ovarian cancer cells alleviated mitochondrial damage without affecting paclitaxel cytotoxicity [44].

In oxaliplatin-induced CIPN models, melatonin prevented the loss of mitochondrial membrane potential (Ψm), promoted nerve regeneration in oxaliplatin-challenged Neuro-2a cells and prevented the loss of nitrosation of proteins and antioxidant enzymes by improving nitrooxidative stress mediated by the chemotherapeutic agent oxaliplatin [45] without interfering with oxaliplatin cytotoxic activity in human colon cancer cell lines. In addition, it has been shown that melatonin can prevent oxaliplatin-induced neuronal apoptosis in rats by increasing the LC3A/3B autophagy pathway in peripheral nerves and dorsal root ganglia (DRG), limit oxaliplatin-induced mitochondrial dysfunction and exert neuroprotective effects by inducing autophagy [45]. At the same time, it also has the unique characteristics of acting as an anti-apoptotic agent in normal cells but inducing damage in tumor cells [46]. In vitro studies showed that pretreatment of human neuroblastoma cells (SH-SY5Y) with melatonin-inhibited oxaliplatin-induced proteolytic activation of caspase-3, inactivation of poly (ADP-ribose) polymerase and DNA damage, thereby rendering resistant apoptotic cells dead, suggesting that melatonin plays a significant role in reducing oxaliplatin-induced neurotoxicity [47]. According to Areti et al. [45], systemic injection of melatonin (3 and 10 mg/kg, i.p.) can prevent oxaliplatin-induced cold and mechanical dysalgesia. In addition, another study reported that both mechanical hyperalgesia and thermal hyperalgesia due to oxaliplatin can be reduced by the use of a higher dose of melatonin (20 mg/kg, i.p.) in rats [48]. At the same time, melatonin treatment significantly inhibited the oxaliplatin-induced increase in the mRNA expression of cytokines such as interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), monocyte chemoattractant protein-1 (MCP-1), and monocyte inflammatory protein-1 (MIP-1α) in the spinal dorsal horn [48].

In vincristine-induced CIPN models, one of the interesting properties of melatonin is that it can rely on its antioxidant properties to enhance the effects of chemotherapeutic drugs (e.g., VCR) [49]. In addition, melatonin could increase catalase (antioxidant enzyme) activity to exert antioxidant effects, protect the sciatic nerve from vincristine-induced degeneration, and enhance the anticancer effect of vincristine; in addition, when melatonin and pregabalin are combined, they have protective and analgesic effects, respectively, and synergistically inhibit vincristine-induced neuropathic pain [50]. Another study showed that a synergistic antitumor effect of melatonin in combination with vincristine or ifosfamide was observed in Ewing sarcoma, the second most frequent type of bone cancer, with significantly elevated activation of caspase-3, -8, -9, and Bid [51]. Preclinical studies have shown that melatonin treatment is well tolerated and has no effects on weight gain, general well-being, and sedation levels in experimental animals [44]. The above studies suggest that melatonin may be an effective prophylactic treatment for patients with chemotherapy-induced painful neuropathy.

Next, in several small clinical studies, melatonin treatment did not affect the effectiveness of chemotherapy in cancer patients [52, 53]. A meta-analysis of 10 randomized controlled trials that included 643 patients with advanced solid tumors using melatonin as the sole therapy or adjuvant therapy reported that melatonin treatment reduced the risk of death at 1 year [54]. Another meta-analysis (8 trials and 761 patients) similarly reported that melatonin as an adjuvant treatment for solid tumor cancers substantially improved tumor remission, 1-year survival, neurotoxicity, and fatigue and alleviated radiochemotherapy-related side effects [55].

In general, short-term use of melatonin is safe, even at extreme doses; similarly, randomized clinical studies have shown that long-term melatonin treatment causes only mild adverse effects comparable to placebo, such as dizziness, nausea, and drowsiness [56]. A randomized, double-blinded, placebo-controlled trial showed that 20 mg of melatonin for breast cancer before and during the first cycle of adjuvant chemotherapy modulated serum levels of brain-derived neurotrophic factor (BDNF) and its receptor tropomyosin kinase B (TrkB), suggesting a neuroprotective effect of melatonin [57]. The results of another randomized, double-blinded, placebo-controlled trial suggest that oral melatonin, combined with the first adjuvant chemotherapy for breast cancer (ACBC), can counteract dysfunction of the inhibitory descending pain regulatory system (DPMS) and reduce serum levels of neuronal and astrocyte neuroplasticity markers (i.e., BDNF, S100B proteins, and TrkB), thus improving pain perception indicators [58]. Thus, further large-scale randomized clinical trials (RCTs) are urgently needed at various clinical sites to verify the therapeutic effect of melatonin in combination with chemotherapeutic drugs and whether melatonin can intervene in chemotherapy-induced neuropathy (Fig. 2).

N-acetylcysteine

N-acetylcysteine (NAC), the acetylated form of l-cysteine, is a sulfhydryl antioxidant [59]. As an antioxidant of the

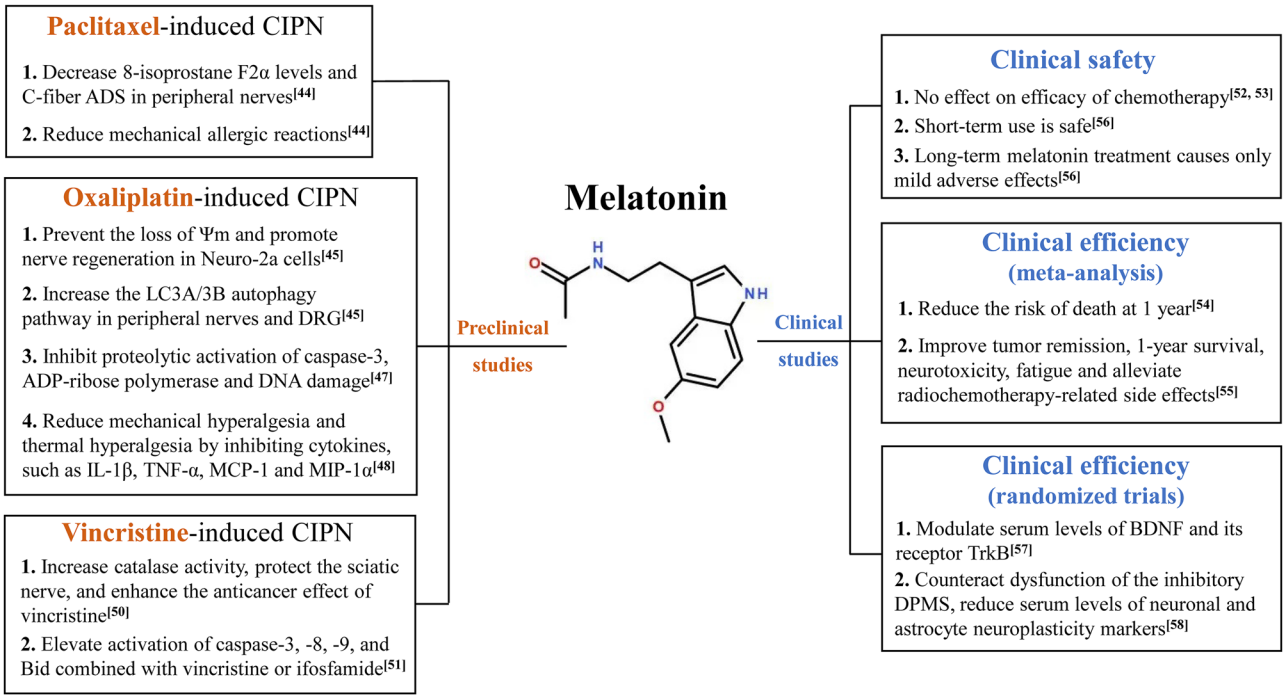

Fig. 2 Available preclinical and clinical evidence for melatonin intervention in CIPN

second line of defense, it may have a protective effect on CIPN by reducing oxidative stress and having free radical elimination activity. Moreover, cysteine is the precursor of hepatic glutathione synthesis, which is able to enter the synthesis pathway of glutathione (a potent natural antioxidant) to increase its whole blood concentration [59, 60]. At present, NAC is a convenient, safe, oral drug that can increase the glutathione content in the blood while also reducing homocysteine levels, and an increase in the latter can lead to neuronal degeneration and severe neuropathy [61].

Oral NAC was effective in preventing oxaliplatin-induced mechanical and cold allodynia in mice and significantly reduced liver, kidney, and spinal cord peroxidation, kidney protein carbonylation, and spinal IL-1b and TNF-α expression induced by oxaliplatin but did not affect the antitumor activity or hematological toxicity of oxaliplatin in vivo [62]. Research data suggest that NAC requires multiple doses to achieve efficacy in oxaliplatin-induced CIPN. Another study pointed out that pretreatment with 100 mg/kg NAC eliminated paclitaxel-induced allodynia in the CIPN mouse model, while in RAW264.7 cells, 50 mM NAC completely blocked the paclitaxel-induced release of high mobility group box 1 (HMGB1) and upregulation of CREB-binding protein (CBP) and p300/CBP-associated factor (PCAF) [63]. According to Nakano et al. [64], NAC can rescue cells from bortezomib-induced peripheral neuropathy (BIPN), and delayed administration of these agents could achieve neuroprotection. In addition, NAC (20 mg/kg) inhibited doxorubicin-induced cold and mechanical hyperalgesia, improved sciatic nerve injury, and reversed plasma malondialdehyde (MDA) levels and total antioxidant capacity (TAC) in CIPN rats [65]. An in vitro experiment using a mouse dorsal root ganglion neuron-neuroblastoma hybrid cell line (N18D3) was performed to investigate the pathological mechanism of cisplatin-induced peripheral neuropathy. The results showed that NAC preincubation exerted a neuroprotective effect against cisplatin-induced neurotoxicity in hybrid neurons mainly by inhibiting the accumulation of p53 but not Fas/Fas-L [66].

Some clinical randomized controlled studies have also assessed the impact of NAC on the incidence and severity of CIPN in patients and its potential preventive role. N-acetylcysteine has been reported to be used at doses ranging from 1200 to 8000 mg/day for 4 weeks to 6 months, with no significant safety issues reported [67]. A prospective randomized controlled open trial of 75 breast cancer patients showed that oral NAC (1200 mg once and twice daily) was effective in reducing the incidence and severity of paclitaxel-induced peripheral neuropathy, accompanied by increased serum nerve growth factor (NGF) levels and decreased malondialdehyde (MDA) levels, which could prevent grade 3 neurotoxicity [68]. In addition, no paclitaxel dose reduction occurred in the NAC group, which is important to improve patient survival and quality of life. Similarly, a small clinical study conducted by Lin et al. on 14 colon cancer patients receiving oxaliplatin-induced adjuvant

chemotherapy reported a lower incidence of peripheral neuropathy in patients receiving daily oral NAC (1200 mg) [59]. In another randomized, double-blind, placebo-controlled clinical trial, 32 patients with colorectal cancer and gastric cancer were randomly given NAC (two 600 mg tablets) or placebo tablets, and NAC was found to reduce the incidence of oxaliplatin-induced neuropathy and delay its occurrence after oxaliplatin chemotherapy [69]. Based on the above research results, it is recommended that larger-scale clinical studies be conducted using different doses of NAC or extending the duration of use to confirm this potential effect of NAC in alleviating CIPN (Table 2).

Vitamins

Vitamin E

It is well known that vitamin E (alpha-tocopherol) is a scavenger of lipid peroxyl radicals, which are widely found in various vegetable oils, nuts and green leafy vegetables, especially in lipophilic microenvironments such as phospholipid membranes [70, 71]. As one of the most widely studied antioxidants (the second line of defense), vitamin E contains tocotrienol and tocopherol, and its most biologically active component is α-tocopherol [72]. It is regarded as a neuropathic treatment and can be used to alleviate chemotherapy-related toxicities [73].

Vitamin E at 50 mg/kg can be a good candidate for the treatment of oxaliplatin-induced CINP (such as mechanical and cold allodynia) in a tumor-bearing mouse model [62]. In addition, indicators of protein oxidation and lipid peroxidation in rats after oxaliplatin treatment showed an increase in carbonylated proteins and thiobarbituric acid reactive substances in plasma, and the same oxidation pattern also reflected in the sciatic nerve and spinal cord reached the DNA level [74]. The study proposed that oxaliplatin-dependent pain induced by mechanical and thermal stimuli was reduced in rats receiving natural antioxidant compounds such as vitamin E and silibinin and that the application of antioxidants was also able to improve motor coordination in CINP rats [74]. These results led the researchers to hypothesize the relationship between the preventive activity of oxidative stress and the anti-hyperalgesic properties of both molecules. Furthermore, another study conducted by the research team in the following year showed that neither vitamin E nor silibinin on neurological-derived cells altered oxaliplatin-induced apoptosis in the human colon adenocarcinoma cell line (HT29), indicating that these antioxidant compounds have different anti-apoptotic characteristics in normal cells versus tumor cells and that data obtained in in vitro cell models parallel in vivo studies [23].

The results of the above animal experimental studies proved the positive effect of vitamin E, which prompted more researchers to seek its effectiveness in clinical trials. It has been proposed that the severity of peripheral neuropathy is inversely proportional to the level of vitamin E, while chemotherapy-induced vitamin E deficiency makes the nervous system more vulnerable. Previous studies showed that vitamin E exhibited beneficial effects in preventing CIPN with a valid and reliable measurement tool [71]. A network meta-analysis pointed out that compared with patients using placebo, patients treated with vitamin E exhibited a lower risk of overall neurotoxicity (though with a considerably large 95% Crl), suggesting that vitamin E should be recommended for the treatment of overall neuropathy [75]. However, vitamin E did not decrease the incidence of CIPN in another meta-analysis of clinical trials, and studies also proposed the need for additional randomized controlled trials using large samples to confirm the effect of vitamin E supplementation [76].

Cancer patients who developed severe neuropathy had significantly lower plasma levels of vitamin E after 2 and 4 cycles of cisplatin treatment. A recent meta-analysis of randomized controlled trials (8 RCTs, involving 488 patients) showed that treatment with vitamin E supplementation at 600 mg/day significantly reduced the incidence of peripheral neuropathy in the cisplatin chemotherapy group; in particular, the gastrocnemius amplitude was significantly reduced in patients treated with vitamin E after 3 rounds of chemotherapy (rather than the 6th round of chemotherapy) and improved the incidence of chemotherapy-induced neurotoxicity, reflexes, and distal paresthesia, which moderately prevented CIPN [77]. Another meta-analysis of 9 randomized controlled trials (RCTs) with 486 patients who compared the vitamin E group with the control group showed a beneficial effect of vitamin E on the incidence and symptoms of CIPN but also proposed that routine prophylactic use of vitamin E is still not recommended [78]. In addition, studies have indicated that vitamin E can be used safely and effectively for CIPN caused by paclitaxel, and routine administration of such supplements without specific side effects may enhance the quality of life in chemotherapy patients [79].

Nevertheless, long-term use of vitamin E and selenium supplements was associated with an increased risk of prostate cancer induction in a prospective multicenter randomized blinded controlled trial of 35,533 men (hazard ratio, 1.17; $p = 0.008$) [80]. Furthermore, a recent study also proposed that if the potential benefits of vitamin E supplementation are further demonstrated in future studies, it is necessary to take into account the risk factors for whether vitamin E supplementation promotes the development of cancer [81]. Numerous CIPN interventions were declared ineffective based on the results of phase III trials. Nonetheless, the internal validity threat of these studies may lead to Type II errors and subsequent dismissal of potentially effective interventions. A systematic review

Table 2 N-acetylcysteine, vitamins, and alpha-lipoic acid with antioxidant activity against CIPN

Agent/compound pharmacologic agent	Chemotherapy drugs	Action/possible mechanism	Outcome	Refs.
N-acetylcysteine	Oxaliplatin	Prevented mechanical and cold allodynia in mice Reduced spinal IL-1β and TNF-α expression in mice	Reduced liver, kidney, and spinal cord peroxidation, kidney protein carbonylation; Had no protective effect on heart tissue	[62]
	Paclitaxel	Blocked HMGB1 release and CBP/PCAF upregulation in RAW264.7 cells Eliminated allodynia in mice	Unveiled NAC as an emerging therapeutic avenue targeting a neuroimmune crosstalk in CIPN	[63]
	Bortezomib	Alleviated the cytotoxicity in Schwann cells but not myeloma cells	Rescued cells from BIPN, and delayed administration could achieve neuroprotection	[64]
	Doxorubicin	Inhibited cold and mechanical hyperalgesia in rats, and reversed MDA and TAC	Had a role in peripheral neuroprotective properties and free radical-induced toxic reduction	[65]
	Cisplatin	Inhibited the accumulation of p53 but not Fas/Fas-L in N18D3 cells	Exerted a neuroprotective effect against neurotoxicity in hybrid neurons	[66]
	Paclitaxel	Reduced the incidence and severity of PIPN; Increased NGF and decreased MDA	Prevented grade 3 neurotoxicity of breast cancer patients	[68]
	Oxaliplatin	Reduced neuropathy in patients with gastric or colorectal cancers	Reported a lower incidence of peripheral neuropathy and delayed CIPN occurrence	[59, 69]
Vitamin E	Oxaliplatin	Prevented mechanical and cold allodynia in mice; Inhibited ROS-dependent neuroinflammation	Inhibited of CIPN without compromising OXA antitumor activity with translational potential	[62]
		Reduced mechanical and thermal stimuli in CINP rats	Established a relationship between the improvement of oxidative alterations and pain relief	[74]
		Not altered oxaliplatin-induced apoptosis in HT29	Had different anti-apoptotic characteristics in normal cells versus tumor cells	[23]
	Cisplatin	Reduced the severity of neurotoxicity of patients	Reduced the relative risk of developing signs or symptoms of neurotoxicity	[71]
		Reduced the incidence of peripheral neuropathy, reflex and distal paresthesia; Improved neurotoxicity scores	Had a beneficial effect on the incidence and symptoms of CIPN; However, routine prophylactic use of vitamin E is still not recommended	[77, 78]
	Paclitaxel	Reduced the incidence of peripheral neuropathy	Had no special side effect and enhanced the quality of life in chemotherapy patients	[79]
Other antioxidant vitamins	Cisplatin	RA failed to prevent the morphometric, electrophysiological, functional, and analytical disturbance induced in rat DRG neurons	Caused only a mild generalized protective effect	[85]
	Cisplatin/ Paclitaxel	ATRA up-regulated NGF and RAR-β expression in mice; Reduced electrophysiological changes and NGF levels in patients with NSCLC	Improved nerve conduction of CIPN	[86]
	Paclitaxel	Vitamin C reduced PICs in rats DRG	Inhibited paclitaxel-induced neuropathic pain	[87]
	Cisplatin	Vitamin C pretreatment exhibited lowered paw withdrawal thresholds	Consistented with the development of cisplatin-induced allodynia, without significant differences	[91]

Table 2 (continued)

Agent/compound pharmacologic agent	Chemotherapy drugs	Action/possible mechanism	Outcome	Refs.
Alpha-Lipoic Acid (ALA)	Paclitaxel/ Cisplatin	Exerted neuroprotective effects by inducing the expression of frataxin	Rescued chemotherapy-induced mitochondrial toxicity	[96]
	Paclitaxel	Ameliorated nab-PTX-induced CIPN through the Nrf2 pathway	Not promoted tumor growth or reduced chemotherapy efficacy	[97]
	Potentially neurotoxic agents	Decreased pain and both sensor and motor neuropathic impairment	Improved CIPN symptoms in a prospective series of patients, with no significant toxicity or interaction	[98]
	Docetaxel	Recovered of neurological symptoms	Reduced in CIPN grade and a median time to remission of 4 weeks	[99]
	Oxaliplatin/ Cisplatin	Ineffective at preventing neurotoxicity	No statistically significant difference in CIPN pain assessments	[100]

IL-1β Interleukin-1β, *TNF-α* Tumor necrosis factor-α, *HMGB1* High mobility group box 1, *CBP* CREB-binding protein, *PCAF* p300/CBP-associated factor, *CIPN* Chemotherapy-induced peripheral neuropathy, *NAC* N-acetylcysteine, *BIPN* Bortezomib-induced peripheral neuropathy, *MDA* Malondialdehyde, *TAC* Total antioxidant capacity, *Fas-L* Fas ligand, *PIPN* Paclitaxel-induced peripheral neuropathy, *NGF* Nerve growth factor, *ROS* Reactive oxygen species, *OXA* Oxaliplatin, *RA* Retinoic acid, *DRG* Dorsal root ganglion, *ATRA* All-trans retinoic acid, *RAR-β* Retinoic acid receptor-β, *NSCLC* Non-small cell lung cancer, *PICs* Proinflammatory cytokines, *PTX* Paclitaxel, *Nrf-2* Nuclear factor E2-related factor 2

proposed that patients may benefit from rigorous retesting of several agents (e.g., drugs such as α-lipoic acid, duloxetine, glutathione, and vitamin E) to extend and validate the evidence of American Society of Clinical Oncology (ASCO) recommendations for CIPN management [82]. Therefore, in view of the controversy of the above studies, more high-quality double-blind RCTs are needed to further verify the effectiveness of vitamin E in preventing CIPN.

Other Antioxidant Vitamins

Retinoic acid (RA), an active metabolite of retinol (vitamin A), has been shown to have neurotrophic effects and is able to induce upregulation of nerve growth factor (NGF), low-affinity $p75^{NGF}$ receptors, and high-affinity receptors for neurotrophin-specific tropomyosin-related kinase (trk) [83, 84]. Preliminary studies on the possible neuroprotective effects of retinoic acid revealed that RA failed to prevent the morphometric, electrophysiological, functional, and analytical disturbance induced in rat DRG neurons and caused only a mild generalized protective effect [85]. In addition, Arrieta et al. [86] reported that all-trans retinoic acid (ATRA) alleviated chemotherapy-induced experimental neuropathy in mice by upregulating NGF levels and retinoic acid receptor (RAR)-β expression. Additionally, ATRA treatment reduced electrophysiological changes and NGF levels in patients with non-small cell lung cancer (NSCLC) receiving standard treatment based on cisplatin and paclitaxel.

The antioxidant vitamin C was reported to have a significant inhibitory effect on paclitaxel-induced neuropathic pain in rats, accompanied by a reduction in proinflammatory cytokines (PICs) in the DRG [87]. Intravenous ascorbic acid (AA, vitamin C) with or without concomitant chemotherapy has been reported in a large number of cancer patients, often in nonconventional healthcare settings [88], and for all patients receiving intravenous AA, symptoms related to pain were significantly improved or stabilized ($p < 0.05$) [89, 90]. However, the long-term effects of vitamin C pretreatment on cisplatin-induced mechanical and cold allodynia were lowered paw withdrawal thresholds, consistent with the development of cisplatin-induced allodynia, without significant differences [91]. Future studies could more deeply evaluate the alleviating effect of vitamins with antioxidant effects on CIPN and improvements in valid quality-of-life measures (Table 2).

Alpha-Lipoic Acid (ALA)

As an essential cofactor for energy production, alpha-lipoic acid (ALA) can act as an effective physiological antioxidant

to exert apoptotic effects on tumor cell lines and has been extensively studied in the treatment of diabetic neuropathy [92, 93]. ALA can neutralize free radicals, increase glutathione synthesis; moreover, this cofactor can regenerate other important antioxidants through dihydrolipoic acid (DHLA), preventing the formation of glycation end products (AGEs) as well as mitochondrial damage by oxidative stress [94, 95].

In a previous study, primary cultures of dorsal root ganglion (DRG) sensory neurons were exposed to paclitaxel and cisplatin in an in vitro chemotherapy-induced peripheral neuropathy model; it was found that ALA exerted neuroprotective effects by inducing the expression of frataxin, an essential mitochondrial protein with antioxidant properties, rescuing chemotherapy-induced mitochondrial toxicity [96]. In rat tumor xenograft models, ALA significantly ameliorated nab-paclitaxel (nab-PTX)-induced CIPN through the Nrf2 signaling pathway ($p < 0.05$) without promoting tumor growth or reducing chemotherapy efficacy [97].

Promising results were obtained in an exploratory study in which ALA in combination with Boswellia and bromelain significantly reduced CIPN in patients over a 12-week regimen [98]. In another study involving 14 cancer patients (10 patients with CIPN grade 2 and 4 patients with CIPN grade 3), a median cumulative docetaxel dose of 400 mg/m^2 was given. ALA 600 mg was administered i.v. weekly for 3–5 weeks, followed by 1800 mg td p.o., until complete recovery of neurological symptoms, with 8 patients having a significant reduction in CIPN grade and a median time to remission of 4 weeks [99]. However, another study evaluating the role of oral ALA in preventing neurotoxicity induced by oxaliplatin or cisplatin showed different results. Of the 243 patients, 70 (29%) completed the study (24 weeks), and no statistically significant difference in CIPN pain assessments was found between the ALA and placebo groups [100]. However, the authors of this study also concluded that the high attrition rate due to poor patient compliance and mode of administration indicated the lack of feasibility of this intervention and suggested another view that ALA should be neglected as a future study of potential prevention of CIPN if innovative methods and trial designs can be identified and pursued. Undoubtedly, future studies should better assess the effect of ALA in preventing or treating CIPN at the experimental level to fully pave the way for any further randomized clinical trials.

In fact, phenomena such as insufficient stability in the stomach, reduced solubility, and hepatic degradation result in a bioavailability of approximately 30% and a short half-life of ALA, whereas intravenous injection of ALA in other models achieves higher bioavailability. The new oral formulation of ALA has been reported to have the potential to overcome these pharmacokinetic limitations because it uses only the R-ALA enantiomer as a liquid solution, making it more soluble and stable in the gastric environment [101, 102]. All these studies suggest that ALA may be beneficial for CIPN, but more in-depth studies are needed (Table 2).

Other Exogenous Antioxidant Supplements: Preclinical and Clinical Perspectives on CIPN Management

Mineral Elements

An in vitro experimental study showed that magnesium (Mg), manganese (Mn), and zinc salts were able to prevent oxaliplatin-induced microglial alterations by reducing oxidative and endoplasmic reticulum stress [103]. Zinc, as a transition metal, has a long history of use as an anti-inflammatory agent. Additionally, its exogenous application has antihyperalgesic effects in multiple inflammatory and neuropathic pain model systems [104, 105]. Recently, zinc has been found to be involved in a novel mechanism of paclitaxel-induced CINP; that is, TRPV1-mediated pain perception can be inhibited by extracellular zinc entry into cells via transient receptor potential A1 (TRPA1) channels or zinc transporters [106].

Selenium, as a trace element, has been shown to have an important role in cellular redox regulation and protection of cellular components from oxidative damage. Selenium administration partially reversed the amplitude of compound action potential, nerve conduction velocity, and the number of axons in rats receiving chemotherapy, which in turn had a moderate neuroprotective effect against cisplatin-induced neurotoxicity [107]. Furthermore, intravenous administration of high-dose selenium enhances the effects of selenium with acceptable toxicity, with adverse events rarely occurring where intravenous selenium was administered at up to 5000 µg/day [108, 109]. Based on this, an investigator-initiated, phase III, double-blind, randomized controlled trial was performed to evaluate the efficacy and safety of high-dose selenium (2000 µg/day) intravenously in a 1:1 ratio for the prevention of CIPN in 68 platinum-sensitive cancer patients treated with paclitaxel, carboplatin, and bevacizumab [110]. The results of this clinical study are not available at present, and further follow-up will be performed.

The hypothesis that increased extracellular Ca/Mg might ameliorate or prevent oxaliplatin-induced neurotoxicity has been confirmed in cell- and animal-based studies without reducing the antitumor activity of oxaliplatin [111, 112]. The results of a systematic review demonstrated the non-beneficial effect of CaMg infusions for the prevention of oxaliplatin-induced peripheral neuropathy. However, the results of a systematic review demonstrated the nonbeneficial effect of Ca/Mg infusion in preventing oxaliplatin-induced CIPN [113]. According to Gamelin

et al. [114], Ca/Mg infusions reduced the intensity and incidence of acute symptoms of oxaliplatin-induced neuropathy in patients. Nevertheless, later studies did not confirm this observation. A phase III, randomized, placebo-controlled, double-blind study of 353 patients with colon cancer receiving adjuvant FOLFOX (leucovorin, fluorouracil and oxaliplatin) randomly assigned to intravenous calcium/magnesium before and after oxaliplatin showed no significant reduction in oxaliplatin-induced acute neuropathy, and the results of this study did not support the use of calcium/magnesium to prevent CIPN [115]. Interestingly, a subsequent study conducted a methodological study analysis of this clinical result. The examination of prior studies resulted in different findings for the same treatment received due to potential confounding variables or biases not considered or not statistically controlled for, as well as considerations of statistical power and analysis, in conjunction with missing data that can affect the outcomes of clinical trials [116] (Fig. 3).

Subsequently, it is necessary to further explore whether mineral elements play an important role in CIPN. Although their efficacy in the treatment of neuropathy is still controversial, the current data indicate that these metals can effectively prevent chemotherapy-induced neurotoxicity in preclinical studies. Sample interference needs to be excluded, and more in-depth and perfect clinical trials need to be verified in the future.

Phytochemicals

Curcumin

Curcumin, a phenolic compound derived from Curcuma longa L. (turmeric), can act as an antioxidant to ameliorate chemotherapy-induced demyelination by reducing oxidative stress while alleviating the structural and functional defects observed in CIPN [117]. A safety evaluation study indicated that curcumin did not have any toxic effects and was well tolerated in the high dose range. In addition, despite some studies on its toxicity, the FDA declared curcumin to be "generally safe" [118, 119]. Furthermore, curcumin tends to accumulate in hydrophobic regions after application, for example, cell membranes, where it acts as a hydrophobic degrader (antioxidant) to scavenge various reactive oxygen species (ROS) and is better than vitamin E in inhibiting oxidative stress [120].

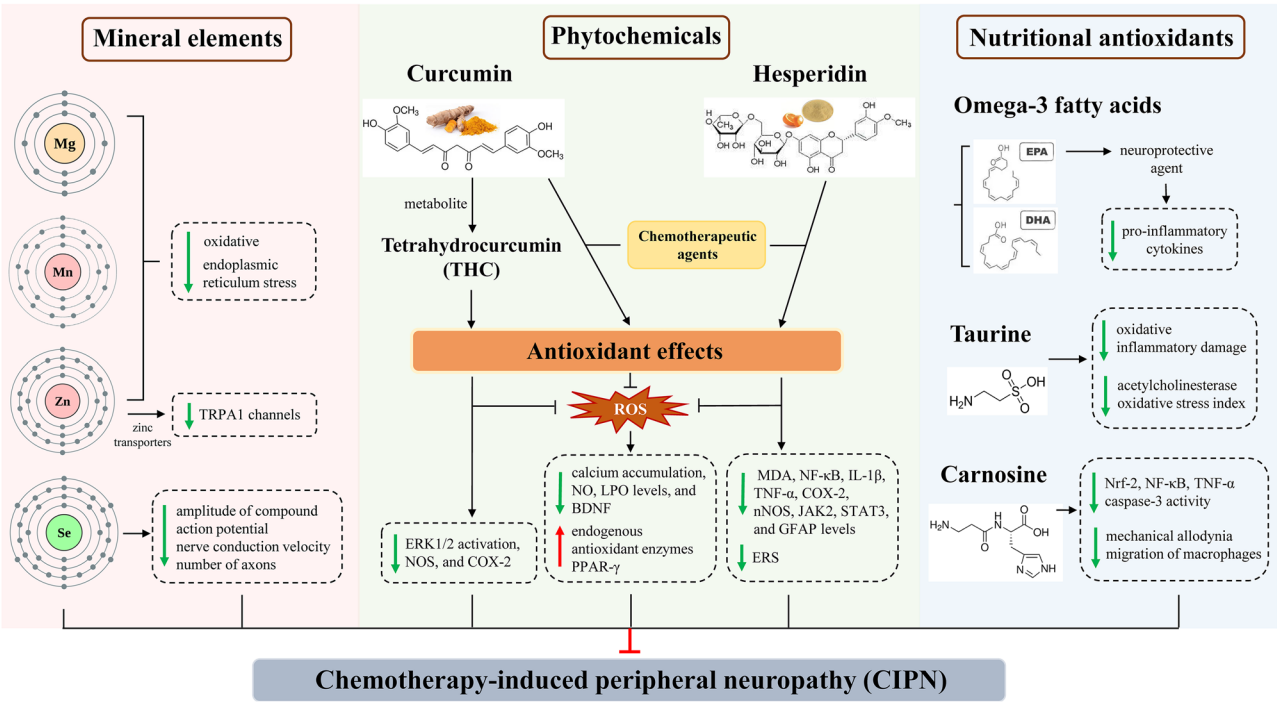

Fig. 3 Schematic diagram of the analgesic effect of other exogenous antioxidant supplements in CIPN. Mg, Magnesium; Mn, Manganese; Zn, Zinc; Se, Selenium; TRPA1, Transient receptor potential A1; ERK1/2, Extracellular signal regulated kinase 1/2; NO/NOS/nNOS, Nitric oxide/Nitric oxide synthase/Neuronal nitric oxide synthase; COX-2, Cyclooxygenase-2; LPO, Lipid peroxidation; BDNF, Brain-derived neurotrophic factor; PPAR-γ, Peroxisome proliferator-activated receptor-γ; MDA, Malondialdehyde; NF-κB, Nuclear factor kappa-B; IL-1β, Interleukin-1β; TNF-α, Tumor necrosis factor-α; JAK2, Janus kinase 2; STAT3, Signal transducer and activator of transcription 3; GFAP, Glial fibrillary acidic protein; ERS, Endoplasmic reticulum stress; EPA, Eicosapentaenoic acid; DHA, Docosahexaenoic acid; Nrf-2, Nuclear factor E2-related factor 2

According to Babu et al. [121], in the vincristine-induced CIPN model, curcumin at doses of 30 and 60 mg/kg significantly increased the nociceptive threshold and levels of endogenous antioxidant enzymes, decreased vincristine-induced calcium accumulation, nitric oxide (NO), and lipid peroxidation (LPO) levels in the sciatic nerve of mice, and exerted analgesic, calcium inhibitory, neuroprotective, and antioxidant effects in a dose-dependent manner, which in turn ameliorated vincristine-induced neuropathy in mice. In addition, curcumin has been shown in studies to significantly decrease LPO and NO and increase endogenous antioxidant enzyme levels better than pregabalin (a selective Cav2.2 channel antagonist) [121]. The antinociceptive effect of curcumin in the delayed phase (peripheral action) and hot plate model (central activity) may be attributed to either the metabolite (tetrahydrocurcumin, THC) or the inhibitory effect on cytokine production or both. Moreover, it has been reported that tetrahydrocurcumin reduces the levels of inducible NOS and cyclooxygenase-2 (COX-2) by downregulating extracellular signal regulated kinase 1/2 (ERK1/2) activation and has better activity than curcumin [122]. Another study pointed out that 80 mg/kg THC significantly reduced vincristine-induced neuropathic pain in rats, and the mechanism may be related to its antinociceptive, anti-inflammatory, neuroprotective, TNF-α inhibitory, calcium inhibitory, and antioxidant activities [123]. The above studies indicate that curcumin and its metabolite THC can be used as promising candidates for CIPN prevention by chemotherapeutic agents.

In CIPN in vivo models induced by cisplatin, postmitotic sensory neurons in the dorsal root ganglion (DRG) are particularly sensitive to cisplatin injury, and axonal damage induced by cisplatin involves multiple events, including ROS generation, suggesting that antioxidants may help reduce the neurotoxicity of cisplatin [124, 125]. In addition, in an in vitro model of PC12 cell neurotoxicity, studies have demonstrated that curcumin can protect PC12 cells from the inhibition of cisplatin without compromising cisplatin's anticancer activity [126]. While loss of p53 function may weaken the apoptotic signaling response mediated by DNA damage related to chemotherapy resistance [127], thinking about strategies to reduce side effects without compromising p53 function will be of widespread value in cancer treatment. Curcumin neither inhibits the transcription of p53 mRNA nor protects tumor cells against the cytotoxic effect of cisplatin on HepG2 cells [126]. Therefore, subsequent clinical studies using curcumin to reduce peripheral neuropathy in patients receiving chemotherapy should be considered.

Curcumin was reported to improve the functional and structural abnormalities of cisplatin-induced neuropathy in rats, such as improving the reduction in sciatic nerve myelin thickness in cisplatin-treated rats and partially blocking nucleolar atrophy [128]. In addition, a similar study reported that curcumin attenuated pain behavior induced by cisplatin and oxaliplatin in rats, reversed the alterations in plasma neurotensin and sciatic nerve platinum concentrations, and significantly improved the histology of the sciatic nerve in rats; these findings indicated that concomitant treatment with curcumin (administered as an added anticancer therapy and neuroprotective agent) may not reduce the therapeutic effect of these platinum agents [129]. Other studies have shown that curcumin attenuated cisplatin-induced nephrotoxicity and enhanced its anticancer activity in SD rats, demonstrating its potential role in breast cancer chemotherapy, and cumulative treatment augmented peroxisome proliferator-activated receptor-γ (PPAR-γ) expression while lessening BDNF expression in mammary tumors [130]. Therefore, the use of curcumin and cisplatin in combination for breast cancer treatment may have profound clinical implications, but further studies are still needed to ensure the effectiveness of this combination therapy in different breast cancer models and clinical treatments.

Hesperidin (HES)

Hesperidin (HES) is a bioflavonoid with antioxidant effects that are widespread in citrus fruits [131, 132]. Administration of 100 or 200 mg/kg/b.w. HES (for 10 days) to CIPN rats significantly reduced PTX-induced increases in MDA, NF-κB, IL-1β, TNF-α, COX-2, nNOS, JAK2, STAT3, and GFAP levels with neuropathic pain and alleviated endoplasmic reticulum stress (ERS) [133]. This study suggested that HES administration could alleviate paclitaxel-induced CIPN and might serve as a promising compound for the treatment of cancer patients for subsequent development (Fig. 3).

Nutritional Antioxidants

Omega-3 Fatty Acids

The omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are incorporated into cellular phospholipid membranes as polyunsaturated fatty acids in the central and peripheral nervous systems [134]. Omega-3 fatty acids exert beneficial effects on neurological diseases by acting on neuronal cells and inhibiting the formation of proinflammatory cytokines involved in CIPN [135]. Ghoreishi et al. [136] found that omega-3 fatty acids may be an effective neuroprotective agent against paclitaxel-induced CIPN. The results of the randomized, double-blind, placebo-controlled trial showed that participants randomized to receive omega-3 fatty acids 640 mg (EPA-10% and DHA-54%) three times daily or placebo throughout the duration of paclitaxel chemotherapy and 1 month afterward. Significant between-group differences were observed in the incidence of CIPN and a

70% reduction in risk in the omega-3 fatty acid group [136]. Breast cancer patients can achieve longer disease-free survival rates with the aid of therapeutic agents. In addition, outcomes not assessed by the study should continue to be validated in the future. A systematic review of omega-3 supplements in patients undergoing chemotherapy and/or radiotherapy proposed that omega-3 fatty acid supplements in combination with conventional chemotherapy would be beneficial only for high-quality methodological studies [137]. A small narrative review summarizing nutritional supplements in CIPN also pointed to the potential of glutamine and omega-3 fatty acids as treatment options for CIPN [138]. However, the role of nutritional supplements in CIPN remains controversial due to the varied mechanisms of neuropathy induced by different antineoplastic drugs and the presence of complex drug interactions, and further research on such drugs is necessary in the future.

Other Nutritional Supplements

Taurine, 2-aminoethanesulfonic acid, is a free intracellular amino acid, and the biosynthesis of taurine in the human body occurs mainly in the liver through the oxidation and decarboxylation of the amino acid cysteine [139]. Taurine has been reported to be chemoprotective against cisplatin-induced cardiotoxicity and renal injury by modulating oxidative and inflammatory damage [140, 141]. Pretreatment with taurine significantly improved behavioral performance and brain antioxidant status in cisplatin-treated rats while reducing acetylcholinesterase activity and the oxidative stress index and eliminating the mediated decrease in dendritic arborization and the mean diameter of rat pyramidal neurons [142]. Studies have suggested that taurine may be a possible protective supplement to reduce cisplatin-induced side effects, including neurotoxicity, in cisplatin-treated patients.

Carnosine is an endogenous dipeptide composed of L-histidine and β-alanine that has antioxidant properties and acts on free radicals, and previous studies have reported its potential neuroprotective capability through antioxidant and anti-inflammatory effects [143]. A prospective randomized controlled study evaluating the potential preventive effect of L-carnosine on acute oxaliplatin neurotoxicity in patients with colorectal cancer enrolled 65 patients and showed that the levels or activities of NFκB (27%) and TNF-α (36.6%) were significantly decreased in the group receiving the FOLFOX-6 regimen (oxaliplatin, 5FU, and leucovorin) with daily oral L-carnosine (500 mg), while L-carnosine as a supplement for patients with CIPN alleviated neuropathic symptoms by decreasing oxidative stress (Nrf-2 and NF-κB pathways) and apoptosis (caspase-3 activity) [144]. Another study investigated whether the zinc complex of L-carnosine, polaprezinc (3 mg/kg, p.o), inhibited paclitaxel-induced mechanical allodynia and migration of macrophages in dorsal root ganglion cells without affecting the antitumor activity exerted by paclitaxel in cell lines and tumor-bearing mice [145] (Fig. 3).

These supplements have very promising results in basic research, and some clinical trials have also been carried out. The obtained results also suggest that nutritional supplements can be further investigated in clinical trials as a combination adjuvant therapy in reducing neuropathy symptoms in CIPN patients.

Cytoprotectants

Amifostine

Amifostine, an analog of cysteamine, is a phosphorylated aminothiol prodrug. As a cell protective antioxidant, amifostine acts by scavenging free radicals, supplying hydrogen ions to free radicals, depleting oxygen, accelerating DNA repair and suppressing Fas/FasL-mediated apoptosis [146]. Amifostine at a dose of 25 mg/kg significantly reduced oxaliplatin-induced c-Fos, nitrotyrosine, and activating transcription factor 3 (ATF3) expression, showing protective effects against nitrosative stress, neuronal hyperactivation and neuronal damage to dorsal root ganglion neurons in mice [147]. The neuroprotective effect of amifostine has been demonstrated in some clinical trials for platinum- and paclitaxel-induced neurotoxicity [148, 149]. A double-blind randomized placebo-controlled trial found that amifostine (740 mg/m^2) improved the sensory neuropathy induced by platinum/taxane-based treatment of ovarian cancer, but there was almost no difference in specific sensory or motor symptoms of self-estimation [150]. Hypotension, hypocalcemia, nausea, vomiting, and sneezing are the most common side effects of amifostine therapy [151], and switching to the subcutaneous route of amifostine at a 1000 mg dose is better tolerated with minor side effects in patients who are poorly tolerated with intravenous administration [152]. Therefore, although amifostine has shown promising findings in protecting against platinum- and/or taxane-induced neurotoxicity, it should also be used with caution when combined with cancer chemotherapeutic agents. Future research needs to further evaluate the protective effect against CIPN while considering its side effects.

Calmangafodipir

Calmangafodipir[Ca4Mn(DPDP)5, proprietary name: PledOx®], a derivative of magnetic resonance imaging contrast agent and cytoprotective agent mangafodipir, is a mitochondrial MnSOD mimetic that helps degrade tissue ROS and cells to survive oxidative stress [153]. Calmangafodipir could effectively protect BALB/c mice from oxaliplatin-induced adverse effects and did not negatively

interfere with oxaliplatin antitumor activity [154]. In a randomized placebo-controlled phase II trial in patients with metastatic colorectal cancer, calmangafodipir at a dose of 5 μmol/kg reduced oxaliplatin-induced delay in the onset and intensity of CIPN symptoms during and after treatment and had no negative impact on progression free survival and overall survival outcomes [155]. Another study showed that calmangafodipir protected against small fiber neuropathy in an oxaliplatin-induced BALB/c mouse model, and interestingly, in addition to consistent with previous findings, calmangafodipir showed a U-shaped effect, with the 10 mg/kg dose less effective than the 2.5 and 10 mg/kg doses [156]. In addition, calmangafodipir blocking both the superoxide generation pathway and the hydroxyl generation pathway is likely to contribute to the beneficial therapeutic characteristics of calmangafodipir [157]. According to the POLAR study, intravenous administration of calmangafodipir and oxaliplatin was too close in time, which may lead to unfavorable redox interactions between Mn2 + and Pt^2, while administration of calmangafodipir 10 min before the start of oxaliplatin infusion in previous mouse studies as well as in a phase II clinical trial (PLIANT) could avoid destructive interactions between calmangafodipir and oxaliplatin [158]. Future research needs to pay attention to this point, and whether calmangafodipir can also protect neuropathy from other chemotherapy drugs remains to be further explored.

Synthetic Compounds

7-Chloro-4-(phenylselanyl) Quinoline (4-PSQ)

7-Chloro-4-(phenylselanyl) quinoline (4-PSQ), a new quinoline derivative containing selenium, has attracted great attention in the field of drug development, and its pharmacological effects are related to antioxidant properties [159, 160]. Several recent studies have shown that 4-PSQ reversed OXA-induced mechanical and thermal hypersensitivity, ameliorated chemotherapy-induced oxidative imbalance by reducing reactive species (RS) levels, normalizing glutathione peroxidase (GPx), catalase (CAT), superoxide dismutase (SOD) and acetylcholinesterase (AChE) activities in all tissues [161], and reversed aging-aggravated by reducing ROS and NOx levels [162]. In another paclitaxel-induced peripheral neuropathy (PIPN), 4-PSQ was observed to decrease paclitaxel-induced mechanical and thermal hypersensitivity, possibly related to modulation of oxidative stress in the spinal cord, hippocampus, and cerebral cortex of PIPN mice [163]. Given that 4-PSQ can act on multiple targets of this pathological change, 4-PSQ could be used as a promising molecular therapy for CIPN. However, more studies as well as clinical trials are needed to determine any long-lasting effects of 4-PSQ as a good prototype on CIPN.

Donepezil

In addition, systemic treatment with donepezil, a centrally active cholinesterase inhibitor, prevented and reversed the cold and mechanical abnormal pain induced by oxaliplatin [164]. The analgesic efficacy of donepezil was also demonstrated in several other CIPN rat models (bortezomib, paclitaxel, and vincristine) and did not alter the viability of cancer cells or the efficacy of anticancer drugs [165]. It has been shown to ameliorate oxaliplatin-induced peripheral neuropathy in rats and effectively attenuate oxaliplatin- and cisplatin-induced inhibition of neurite outgrowth in cultured PC12 cells without impairing anticancer efficacy, in which donepezil recovered oxaliplatin-induced reduction in SOD activity and exerted antioxidant effects [166]. Meanwhile, another study also confirmed that the intervention of donepezil combination therapy reduced doxorubicin-induced neuroinflammation and cerebral oxidative stress as well as restored mitochondrial homeostasis without altering the anticancer properties of doxorubicin in the breast cancer phenotype [167]. The DONEPEZOX trial, as a proof-of-concept, randomized, triple-blind, and multicenter study, will be the first clinical trial to evaluate the efficacy and safety of donepezil in oxaliplatin for gastrointestinal cancer-induced severe peripheral neuropathy (OIPN), with the response rate in the donepezil group (neuropathy grade reduction according to the QLQ-CIPN20 sensory score) as the primary endpoint [168]. The final results of this study will provide new considerations and basis for the further clinical application of donepezil, as the analgesic effect of donepezil was verified in different animal models of CIPN and was associated with its oncological safety. Next, clinical trials can be initiated for proof-of-concept validation.

In summary, the protective effects exerted by synthetic compounds with antioxidant effects in CIPN may provide new ideas for alleviating CIPN patients. Current research may be more limited to specific types of CIPN, and further research and verification are needed to precisely define these effects.

Limitations

There are some limitations to this review that warrant discussion. First, it is unfortunate that no clear indication of the impact of age and gender has been demonstrated in current studies. Second, some clinical studies have potential limitations due to the limited number of cancer patients participating in the study and the lack of long-term follow-up of measured outcomes. Third, the role of some antioxidants in CIPN remains controversial due to the varied mechanisms of neuropathy induced by different chemotherapeutic agents, as well as the presence of complex drug interactions.

In conclusion, the use of antioxidants in combination with chemotherapeutic agents for cancer therapy may have far-reaching clinical implications, and preclinical exploration coupled with larger multicenter clinical studies are urgently needed in the future to verify the effectiveness of this therapy.

Conclusions

Overall, with increased overall survival (progression-free) in cancer patients, CIPN represents an important challenge that interferes with patients' quality of life and drug therapy. Interrupting drug therapy in cancer patients due to the development of CIPN can affect clinically meaningful chemotherapy doses and further treatment. Unfortunately, many older agents causing CIPN remain the mainstay of cancer therapy. For this purpose, we intentionally demonstrate the previously reported effects of various antioxidants in the treatment of CIPN, such as melatonin and NAC, with current evidence from preclinical and clinical studies, showing that they can improve mechanical allodynia and related pain perception indicators; however, more well-designed large-scale RCTs are still needed to verify that chemotherapy-induced vitamin E deficiency makes the nervous system more vulnerable. ALA may rescue chemotherapy-induced mitochondrial toxicity to exert neuroprotective effects, but because of the differences in its in vivo experimental findings, future studies of ALA as a potential prevention of CIPN should not be ignored, while other exogenous antioxidant supplements, such as mineral elements, phytochemicals (curcumin and hesperidin), nutritional antioxidants, cytoprotectants and synthetic compounds, have very promising results in basic research. Furthermore, several clinical trials have also been conducted to confirm their possible efficacy, and multiple studies have confirmed that these antioxidants are critical to cancer therapy in alleviating CIPN without compromising the antitumor efficacy of chemotherapy. In summary, future studies should analyze the protective effects of specific antioxidants more precisely to increase the coverage and precision of prevention and treatment strategies for adverse effects caused by chemotherapy regimens.

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Declarations

Conflict of Interest The authors declare no competing interests.

References

1. Shah A, Hoffman EM, Mauermann ML, et al. Incidence and disease burden of chemotherapy-induced peripheral neuropathy in a population-based cohort. J Neurol Neurosurg Psychiatry. 2018;89:636–41.
2. Banach M, Juranek JK, Zygulska AL. Chemotherapy-induced neuropathies-a growing problem for patients and health care providers. Brain Behav. 2017;7:e00558.
3. Aromolaran KA, Goldstein PA. Ion channels and neuronal hyperexcitability in chemotherapy-induced peripheral neuropathy; cause and effect? Mol Pain. 2017;13:1744806917714693.
4. Grisold W, Cavaletti G, Windebank AJ. Peripheral neuropathies from chemotherapeutics and targeted agents: diagnosis, treatment, and prevention. Neuro Oncol. 2012;14(Suppl 4):iv45-54.
5. Hu S, Huang KM, Adams EJ, Loprinzi CL, Lustberg MB. Recent developments of novel pharmacologic therapeutics for prevention of chemotherapy-induced peripheral neuropathy. Clin Cancer Res. 2019;25:6295–301.
6. Boyette-Davis JA, Cata JP, Driver LC, et al. Persistent chemoneuropathy in patients receiving the plant alkaloids paclitaxel and vincristine. Cancer Chemother Pharmacol. 2013;71:619–26.
7. Krishnan AV, Goldstein D, Friedlander M, Kiernan MC. Oxaliplatin-induced neurotoxicity and the development of neuropathy. Muscle Nerve. 2005;32:51–60.
8. Fehrenbacher JC. Chemotherapy-induced peripheral neuropathy. Prog Mol Biol Transl Sci. 2015;131:471–508.
9. Staff NP, Grisold A, Grisold W, Windebank AJ. Chemotherapy-induced peripheral neuropathy: a current review. Ann Neurol. 2017;81:772–81.
10. Brugnoletti F, Morris EB, Laningham FH, et al. Recurrent intrathecal methotrexate induced neurotoxicity in an adolescent with acute lymphoblastic leukemia: serial clinical and radiologic findings. Pediatr Blood Cancer. 2009;52:293–5.
11. Moreau P, Pylypenko H, Grosicki S, et al. Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: a randomised, phase 3, non-inferiority study. Lancet Oncol. 2011;12:431–40.
12. Hershman DL, Lacchetti C, Dworkin RH, et al. Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2014;32:1941–67.
13. Smith EM, Pang H, Cirrincione C, et al. Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: a randomized clinical trial. JAMA. 2013;309:1359–67.
14. Conklin KA. Chemotherapy-associated oxidative stress: impact on chemotherapeutic effectiveness. Integr Cancer Ther. 2004;3:294–300.
15. Areti A, Yerra VG, Naidu V, Kumar A. Oxidative stress and nerve damage: role in chemotherapy induced peripheral neuropathy. Redox Biol. 2014;2:289–95.
16. Xiao WH, Bennett GJ. Effects of mitochondrial poisons on the neuropathic pain produced by the chemotherapeutic agents, paclitaxel and oxaliplatin. Pain. 2012;153:704–9.
17. Argyriou AA, Bruna J, Marmiroli P, Cavaletti G. Chemotherapy-induced peripheral neurotoxicity (CIPN): an update. Crit Rev Oncol Hematol. 2012;82:51–77.

18. Low PA, Nickander KK, Tritschler HJ. The roles of oxidative stress and antioxidant treatment in experimental diabetic neuropathy. Diabetes. 1997;46(Suppl 2):S38-42.
19. Carvalho LF, Silva AMF, Carvalho AA. The use of antioxidant agents for chemotherapy-induced peripheral neuropathy treatment in animal models. Clin Exp Pharmacol Physiol. 2017;44:971–9.
20. Lim SC, Choi JE, Kang HS, Han SI. Ursodeoxycholic acid switches oxaliplatin-induced necrosis to apoptosis by inhibiting reactive oxygen species production and activating p53-caspase 8 pathway in HepG2 hepatocellular carcinoma. Int J Cancer. 2010;126:1582–95.
21. Nassini R, Gees M, Harrison S, et al. Oxaliplatin elicits mechanical and cold allodynia in rodents via TRPA1 receptor stimulation. Pain. 2011;152:1621–31.
22. Kang L, Tian Y, Xu S, Chen H. Oxaliplatin-induced peripheral neuropathy: clinical features, mechanisms, prevention and treatment. J Neurol. 2021;268:3269–82.
23. Di Cesare ML, Zanardelli M, Failli P, Ghelardini C. Oxaliplatin-induced oxidative stress in nervous system-derived cellular models: could it correlate with in vivo neuropathy? Free Radic Biol Med. 2013;61:143–50.
24. Waseem M, Kaushik P, Tabassum H, Parvez S. Role of mitochondrial mechanism in chemotherapy-induced peripheral neuropathy. Curr Drug Metab. 2018;19:47–54.
25. Sharawy N, Rashed L, Youakim MF. Evaluation of multineuroprotective effects of erythropoietin using cisplatin induced peripheral neurotoxicity model. Exp Toxicol Pathol. 2015;67:315–22.
26. Shim HS, Bae C, Wang J, et al. Peripheral and central oxidative stress in chemotherapy-induced neuropathic pain. Mol Pain. 2019;15:1744806919840098.
27. Duggett NA, Griffiths LA, McKenna OE, et al. Oxidative stress in the development, maintenance and resolution of paclitaxel-induced painful neuropathy. Neuroscience. 2016;333:13–26.
28. Zhang K, Xu Y. Suppressing BRD4 exhibits protective effects against vincristine-induced peripheral neuropathy by alleviating inflammation and oxidative stress. Biochem Biophys Res Commun. 2020;532:271–9.
29. Zheng H, Xiao WH, Bennett GJ. Mitotoxicity and bortezomib-induced chronic painful peripheral neuropathy. Exp Neurol. 2012;238:225–34.
30. Stankovic JSK, Selakovic D, Mihailovic V, Rosic G. Antioxidant supplementation in the treatment of neurotoxicity induced by platinum-based chemotherapeutics-a review. Int J Mol Sci. 2020;21:7753.
31. Ighodaro OM, Akinloye OA. First line defence antioxidants-superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPX): their fundamental role in the entire antioxidant defence grid. Alexandria J Med. 2019;54:287–93.
32. Neha K, Haider MR, Pathak A, Yar MS. Medicinal prospects of antioxidants: a review. Eur J Med Chem. 2019;178:687–704.
33. Mironczuk-Chodakowska I, Witkowska AM, Zujko ME. Endogenous non-enzymatic antioxidants in the human body. Adv Med Sci. 2018;63:68–78.
34. Warraich UE, Hussain F, Kayani HUR. Aging - oxidative stress, antioxidants and computational modeling. Heliyon. 2020;6:e04107.
35. Harris IS, DeNicola GM. The complex interplay between antioxidants and ROS in cancer. Trends Cell Biol. 2020;30:440–51.
36. Carocho M, Morales P, Ferreira ICFR. Antioxidants: reviewing the chemistry, food applications, legislation and role as preservatives. Trends Food Sci Technol. 2018;71:107–20.
37. Tamura H, Kawamoto M, Sato S, et al. Long-term melatonin treatment delays ovarian aging. J Pineal Res. 2017;62.
38. Wang X, Sirianni A, Pei Z, et al. The melatonin MT1 receptor axis modulates mutant Huntingtin-mediated toxicity. J Neurosci. 2011;31:14496–507.
39. Gbahou F, Cecon E, Viault G, et al. Design and validation of the first cell-impermeant melatonin receptor agonist. Br J Pharmacol. 2017;174:2409–21.
40. Lowes DA, Almawash AM, Webster NR, Reid VL, Galley HF. Melatonin and structurally similar compounds have differing effects on inflammation and mitochondrial function in endothelial cells under conditions mimicking sepsis. Br J Anaesth. 2011;107:193–201.
41. Reiter RJ, Mayo JC, Tan DX, Sainz RM, Alatorre-Jimenez M, Qin L. Melatonin as an antioxidant: under promises but over delivers. J Pineal Res. 2016;61:253–78.
42. Favero G, Moretti E, Bonomini F, Reiter RJ, Rodella LF, Rezzani R. Promising antineoplastic actions of melatonin. Front Pharmacol. 2018;9:1086.
43. Sanchez-Hidalgo M, Lee M, de la Lastra CA, Guerrero JM, Packham G. Melatonin inhibits cell proliferation and induces caspase activation and apoptosis in human malignant lymphoid cell lines. J Pineal Res. 2012;53:366–73.
44. Galley HF, McCormick B, Wilson KL, Lowes DA, Colvin L, Torsney C. Melatonin limits paclitaxel-induced mitochondrial dysfunction in vitro and protects against paclitaxel-induced neuropathic pain in the rat. J Pineal Res. 2017;63:e12444.
45. Areti A, Komirishetty P, Akuthota M, Malik RA, Kumar A. Melatonin prevents mitochondrial dysfunction and promotes neuroprotection by inducing autophagy during oxaliplatin-evoked peripheral neuropathy. J Pineal Res. 2017;62:e12393.
46. Sainz RM, Mayo JC, Rodriguez C, Tan DX, Lopez-Burillo S, Reiter RJ. Melatonin and cell death: differential actions on apoptosis in normal and cancer cells. Cell Mol Life Sci. 2003;60:1407–26.
47. Waseem M, Sahu U, Salman M, et al. Melatonin pre-treatment mitigates SHSY-5Y cells against oxaliplatin induced mitochondrial stress and apoptotic cell death. PLoS ONE. 2017;12:e0180953.
48. Wang YS, Li YY, Cui W, et al. Melatonin attenuates pain hypersensitivity and decreases astrocyte-mediated spinal neuroinflammation in a rat model of oxaliplatin-induced pain. Inflammation. 2017;40:2052–61.
49. Hardeland R. Antioxidative protection by melatonin: multiplicity of mechanisms from radical detoxification to radical avoidance. Endocrine. 2005;27:119–30.
50. Soliman A, Wahid A, Wahby MM, Bassiouny A. Study of the possible synergistic protective effects of Melatonin and Pregabalin in Vincristine induced peripheral neuropathy Wistar Albino rats. Life Sci. 2020;244:117095.
51. Casado-Zapico S, Rodriguez-Blanco J, Garcia-Santos G, et al. Synergistic antitumor effect of melatonin with several chemotherapeutic drugs on human Ewing sarcoma cancer cells: potentiation of the extrinsic apoptotic pathway. J Pineal Res. 2010;48:72–80.
52. Sookprasert A, Johns NP, Phunmanee A, et al. Melatonin in patients with cancer receiving chemotherapy: a randomized, double-blind, placebo-controlled trial. Anticancer Res. 2014;34:7327–37.
53. Nahleh Z, Pruemer J, Lafollette J, Sweany S. Melatonin, a promising role in taxane-related neuropathy. Clin Med Insights Oncol. 2010;4:35–41.
54. Mills E, Wu P, Seely D, Guyatt G. Melatonin in the treatment of cancer: a systematic review of randomized controlled trials and meta-analysis. J Pineal Res. 2005;39:360–6.
55. Wang YM, Jin BZ, Ai F, et al. The efficacy and safety of melatonin in concurrent chemotherapy or radiotherapy for solid tumors: a meta-analysis of randomized controlled trials. Cancer Chemother Pharmacol. 2012;69:1213–20.
56. Andersen LP, Gogenur I, Rosenberg J, Reiter RJ. The safety of melatonin in humans. Clin Drug Investig. 2016;36:169–75.
57. Palmer ACS, Zortea M, Souza A, et al. Clinical impact of melatonin on breast cancer patients undergoing chemotherapy;

effects on cognition, sleep and depressive symptoms: a randomized, double-blind, placebo-controlled trial. PLoS ONE. 2020;15:e0231379.
58. Palmer ACS, Souza A, Dos Santos VS, et al. The effects of melatonin on the descending pain inhibitory system and neural plasticity markers in breast cancer patients receiving chemotherapy: randomized, double-blinded, placebo-controlled trial. Front Pharmacol. 2019;10:1382.
59. Lin PC, Lee MY, Wang WS, et al. N-acetylcysteine has neuroprotective effects against oxaliplatin-based adjuvant chemotherapy in colon cancer patients: preliminary data. Support Care Cancer. 2006;14:484–7.
60. Li J, Xu L, Deng X, et al. N-acetyl-cysteine attenuates neuropathic pain by suppressing matrix metalloproteinases. Pain. 2016;157:1711–23.
61. Cascinu S, Catalano V, Cordella L, et al. Neuroprotective effect of reduced glutathione on oxaliplatin-based chemotherapy in advanced colorectal cancer: a randomized, double-blind, placebo-controlled trial. J Clin Oncol. 2002;20:3478–83.
62. Agnes JP, Santos VWD, das Neves RN, et al. Antioxidants improve oxaliplatin-induced peripheral neuropathy in tumor-bearing mice model: role of spinal cord oxidative stress and inflammation. J Pain. 2021;22:996–1013.
63. Sekiguchi F, Domoto R, Nakashima K, et al. Paclitaxel-induced HMGB1 release from macrophages and its implication for peripheral neuropathy in mice: evidence for a neuroimmune crosstalk. Neuropharmacology. 2018;141:201–13.
64. Nakano A, Abe M, Oda A, et al. Delayed treatment with vitamin C and N-acetyl-L-cysteine protects Schwann cells without compromising the anti-myeloma activity of bortezomib. Int J Hematol. 2011;93:727–35.
65. Farshid AA, Tamaddonfard E, Najafi S. Effects of histidine and n-acetylcysteine on experimental lesions induced by doxorubicin in sciatic nerve of rats. Drug Chem Toxicol. 2015;38:436–41.
66. Park SA, Choi KS, Bang JH, Huh K, Kim SU. Cisplatin-induced apoptotic cell death in mouse hybrid neurons is blocked by antioxidants through suppression of cisplatin-mediated accumulation of p53 but not of Fas/Fas ligand. J Neurochem. 2000;75:946–53.
67. Coles LD, Tuite PJ, Oz G, et al. Repeated-dose oral N-acetylcysteine in Parkinson's disease: pharmacokinetics and effect on brain glutathione and oxidative stress. J Clin Pharmacol. 2018;58:158–67.
68. Khalefa HG, Shawki MA, Aboelhassan R, El Wakeel LM. Evaluation of the effect of N-acetylcysteine on the prevention and amelioration of paclitaxel-induced peripheral neuropathy in breast cancer patients: a randomized controlled study. Breast Cancer Res Treat. 2020;183:117–25.
69. Bondad N, Boostani R, Barri A, Elyasi S, Allahyari A. Protective effect of N-acetylcysteine on oxaliplatin-induced neurotoxicity in patients with colorectal and gastric cancers: a randomized, double blind, placebo-controlled, clinical trial. J Oncol Pharm Pract. 2020;26:1575–82.
70. Argyriou AA, Chroni E, Koutras A, et al. Preventing paclitaxel-induced peripheral neuropathy: a phase II trial of vitamin E supplementation. J Pain Symptom Manage. 2006;32:237–44.
71. Pace A, Giannarelli D, Galie E, et al. Vitamin E neuroprotection for cisplatin neuropathy: a randomized, placebo-controlled trial. Neurology. 2010;74:762–6.
72. Malik A, Eggersdorfer M, Trilok-Kumar G. Vitamin E status in healthy population in Asia: a review of current literature. Int J Vitam Nutr Res. 2021;91:356–69.
73. Granados-Principal S, Quiles JL, Ramirez-Tortosa CL, Sanchez-Rovira P, Ramirez-Tortosa MC. New advances in molecular mechanisms and the prevention of adriamycin toxicity by antioxidant nutrients. Food Chem Toxicol. 2010;48:1425–38.
74. Di Cesare ML, Zanardelli M, Failli P, Ghelardini C. Oxaliplatin-induced neuropathy: oxidative stress as pathological mechanism. Protective effect of silibinin. J Pain. 2012;13:276–84.
75. Fu X, Wu H, Li J, et al. Efficacy of drug interventions for chemotherapy-induced chronic peripheral neurotoxicity: a network meta-analysis. Front Neurol. 2017;8:223.
76. Huang H, He M, Liu L, Huang L. Vitamin E does not decrease the incidence of chemotherapy-induced peripheral neuropathy: a meta-analysis. Contemp Oncol (Pozn). 2016;20:237–41.
77. Miao H, Li R, Chen D, et al. Protective effects of Vitamin E on chemotherapy-induced peripheral neuropathy: a meta-analysis of randomized controlled trials. Ann Nutr Metab. 2021;77:127–37.
78. Chen J, Shan H, Yang W, Zhang J, Dai H, Ye Z. Vitamin E for the prevention of chemotherapy-induced peripheral neuropathy: a meta-analysis. Front Pharmacol. 2021;12:684550.
79. Anoushirvani AA, Poorsaadat L, Aghabozorgi R, Kasravi M. Comparison of the effects of Omega 3 and Vitamin E on palcitaxel-induced peripheral neuropathy. Open Access Maced J Med Sci. 2018;6:1857–61.
80. Klein EA, Thompson IM Jr, Tangen CM, et al. Vitamin E and the risk of prostate cancer: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA. 2011;306:1549–56.
81. Samuels N, Ben-Arye E. Integrative approaches to chemotherapy-induced peripheral neuropathy. Curr Oncol Rep. 2020;22:23.
82. Lee D, Kanzawa-Lee G, Knoerl R, Wyatt G, Smith EML. Characterization of internal validity threats to phase III clinical trials for chemotherapy-induced peripheral neuropathy management: a systematic review. Asia Pac J Oncol Nurs. 2019;6:318–32.
83. von Holst A, Rodriguez-Tebar A, Michaille JJ, et al. Retinoic acid-mediated increase in TrkA expression is sufficient to elicit NGF-dependent survival of sympathetic neurons. Mol Cell Neurosci. 1995;6:185–98.
84. Kaplan DR, Matsumoto K, Lucarelli E, Thiele CJ. Induction of TrkB by retinoic acid mediates biologic responsiveness to BDNF and differentiation of human neuroblastoma cells. Eukaryotic Signal Transduction Group. Neuron. 1993;11:321–31.
85. Tredici G, Tredici S, Fabbrica D, Minoia C, Cavaletti G. Experimental cisplatin neuronopathy in rats and the effect of retinoic acid administration. J Neurooncol. 1998;36:31–40.
86. Arrieta O, Hernandez-Pedro N, Fernandez-Gonzalez-Aragon MC, et al. Retinoic acid reduces chemotherapy-induced neuropathy in an animal model and patients with lung cancer. Neurology. 2011;77:987–95.
87. Miao H, Xu J, Xu D, Ma X, Zhao X, Liu L. Nociceptive behavior induced by chemotherapeutic paclitaxel and beneficial role of antioxidative pathways. Physiol Res. 2019;68:491–500.
88. Padayatty SJ, Sun AY, Chen Q, Espey MG, Drisko J, Levine M. Vitamin C: intravenous use by complementary and alternative medicine practitioners and adverse effects. PLoS ONE. 2010;5:e11414.
89. Bazzan AJ, Zabrecky G, Wintering N, Newberg AB, Monti DA. Retrospective evaluation of clinical experience with intravenous ascorbic acid in patients with cancer. Integr Cancer Ther. 2018;17:912–20.
90. Carr AC, Vissers MC, Cook JS. The effect of intravenous vitamin C on cancer- and chemotherapy-related fatigue and quality of life. Front Oncol. 2014;4:283.
91. Guindon J, Deng L, Fan B, Wager-Miller J, Hohmann AG. Optimization of a cisplatin model of chemotherapy-induced peripheral neuropathy in mice: use of vitamin C and sodium bicarbonate pretreatments to reduce nephrotoxicity and improve animal health status. Mol Pain. 2014;10:56.
92. Kamarudin MN, Mohd Raflee NA, Hussein SS, Lo JY, Supriady H, Abdul KH. (R)-(+)-alpha-lipoic acid protected NG108-15 cells against H(2)O(2)-induced cell death through PI3K-Akt/

GSK-3beta pathway and suppression of NF-kappabeta-cytokines. Drug Des Devel Ther. 2014;8:1765–80.
93. Brami C, Bao T, Deng G. Natural products and complementary therapies for chemotherapy-induced peripheral neuropathy: a systematic review. Crit Rev Oncol Hematol. 2016;98:325–34.
94. Dinicola S, Fuso A, Cucina A, et al. Natural products - alpha-lipoic acid and acetyl-L-carnitine - in the treatment of chemotherapy-induced peripheral neuropathy. Eur Rev Med Pharmacol Sci. 2018;22:4739–54.
95. Jones W, Li X, Qu ZC, Perriott L, Whitesell RR, May JM. Uptake, recycling, and antioxidant actions of alpha-lipoic acid in endothelial cells. Free Radic Biol Med. 2002;33:83–93.
96. Melli G, Taiana M, Camozzi F, et al. Alpha-lipoic acid prevents mitochondrial damage and neurotoxicity in experimental chemotherapy neuropathy. Exp Neurol. 2008;214:276–84.
97. Sun H, Guo X, Wang Z, et al. Alphalipoic acid prevents oxidative stress and peripheral neuropathy in Nab-Paclitaxel-treated rats through the Nrf2 signalling pathway. Oxid Med Cell Longev. 2019;2019:3142732.
98. Desideri I, Francolini G, Becherini C, et al. Use of an alpha lipoic, methylsulfonylmethane and bromelain dietary supplement (Opera((R))) for chemotherapy-induced peripheral neuropathy management, a prospective study. Med Oncol. 2017;34:46.
99. Gedlicka C, Kornek GV, Schmid K, Scheithauer W. Amelioration of docetaxel/cisplatin induced polyneuropathy by alpha-lipoic acid. Ann Oncol. 2003;14:339–40.
100. Guo Y, Jones D, Palmer JL, et al. Oral alpha-lipoic acid to prevent chemotherapy-induced peripheral neuropathy: a randomized, double-blind, placebo-controlled trial. Support Care Cancer. 2014;22:1223–31.
101. McIlduff CE, Rutkove SB. Critical appraisal of the use of alpha lipoic acid (thioctic acid) in the treatment of symptomatic diabetic polyneuropathy. Ther Clin Risk Manag. 2011;7:377–85.
102. Brufani M, Figliola R. (R)-alpha-lipoic acid oral liquid formulation: pharmacokinetic parameters and therapeutic efficacy. Acta Biomed. 2014;85:108–15.
103. Branca JJV, Carrino D, Paternostro F, et al. Antioxidant support to ameliorate the oxaliplatin-dependent microglial alteration: morphological and molecular study. Eur J Histochem. 2021;65:3285.
104. Nozaki C, Vergnano AM, Filliol D, et al. Zinc alleviates pain through high-affinity binding to the NMDA receptor NR2A subunit. Nat Neurosci. 2011;14:1017–22.
105. Safieh-Garabedian B, Poole S, Allchorne A, Kanaan S, Saade N, Woolf CJ. Zinc reduces the hyperalgesia and upregulation of NGF and IL-1 beta produced by peripheral inflammation in the rat. Neuropharmacology. 1996;35:599–603.
106. Luo J, Bavencoffe A, Yang P, et al. Zinc inhibits TRPV1 to alleviate chemotherapy-induced neuropathic pain. J Neurosci. 2018;38:474–83.
107. Erken HA, Koc ER, Yazici H, Yay A, Onder GO, Sarici SF. Selenium partially prevents cisplatin-induced neurotoxicity: a preliminary study. Neurotoxicology. 2014;42:71–5.
108. Fakih MG, Pendyala L, Brady W, et al. A Phase I and pharmacokinetic study of selenomethionine in combination with a fixed dose of irinotecan in solid tumors. Cancer Chemother Pharmacol. 2008;62:499–508.
109. Song M, Kumaran MN, Gounder M, et al. Phase I trial of selenium plus chemotherapy in gynecologic cancers. Gynecol Oncol. 2018;150:478–86.
110. Park SJ, Yim GW, Paik H, et al. Efficacy and safety of intravenous administration of high-dose selenium for preventing chemotherapy-induced peripheral neuropathy in platinum-sensitive recurrent ovarian, fallopian or primary peritoneal cancer: study protocol for a phase III, double-blind, randomized study. J Gynecol Oncol. 2021;32:e73.
111. Takeshita M, Banno Y, Nakamura M, et al. The pivotal role of intracellular calcium in oxaliplatin-induced inhibition of neurite outgrowth but not cell death in differentiated PC12 cells. Chem Res Toxicol. 2011;24:1845–52.
112. Sakurai M, Egashira N, Kawashiri T, Yano T, Ikesue H, Oishi R. Oxaliplatin-induced neuropathy in the rat: involvement of oxalate in cold hyperalgesia but not mechanical allodynia. Pain. 2009;147:165–74.
113. Jordan B, Jahn F, Beckmann J, Unverzagt S, Muller-Tidow C, Jordan K. Calcium and Magnesium infusions for the prevention of oxaliplatin-induced peripheral neurotoxicity: a systematic review. Oncology. 2016;90:299–306.
114. Gamelin L, Boisdron-Celle M, Delva R, et al. Prevention of oxaliplatin-related neurotoxicity by calcium and magnesium infusions: a retrospective study of 161 patients receiving oxaliplatin combined with 5-Fluorouracil and leucovorin for advanced colorectal cancer. Clin Cancer Res. 2004;10:4055–61.
115. Loprinzi CL, Qin R, Dakhil SR, et al. Phase III randomized, placebo-controlled, double-blind study of intravenous calcium and magnesium to prevent oxaliplatin-induced sensory neurotoxicity (N08CB/Alliance). J Clin Oncol. 2014;32:997–1005.
116. Visovsky C. Calcium and magnesium for oxaliplatin-induced neurotoxicity: issues in study design, measurement, and analysis. J Adv Pract Oncol. 2015;6:272–6.
117. Oveissi V, Ram M, Bahramsoltani R, et al. Medicinal plants and their isolated phytochemicals for the management of chemotherapy-induced neuropathy: therapeutic targets and clinical perspective. Daru. 2019;27:389–406.
118. Sun J, Chen F, Braun C, et al. Role of curcumin in the management of pathological pain. Phytomedicine. 2018;48:129–40.
119. Sharma S, Kulkarni SK, Agrewala JN, Chopra K. Curcumin attenuates thermal hyperalgesia in a diabetic mouse model of neuropathic pain. Eur J Pharmacol. 2006;536:256–61.
120. Shishodia S, Sethi G, Aggarwal BB. Curcumin: getting back to the roots. Ann N Y Acad Sci. 2005;1056:206–17.
121. Babu A, Prasanth KG, Balaji B. Effect of curcumin in mice model of vincristine-induced neuropathy. Pharm Biol. 2015;53:838–48.
122. Lai CS, Wu JC, Yu SF, et al. Tetrahydrocurcumin is more effective than curcumin in preventing azoxymethane-induced colon carcinogenesis. Mol Nutr Food Res. 2011;55:1819–28.
123. Greeshma N, Prasanth KG, Balaji B. Tetrahydrocurcumin exerts protective effect on vincristine induced neuropathy: behavioral, biochemical, neurophysiological and histological evidence. Chem Biol Interact. 2015;238:118–28.
124. Carozzi VA, Marmiroli P, Cavaletti G. The role of oxidative stress and anti-oxidant treatment in platinum-induced peripheral neurotoxicity. Curr Cancer Drug Targets. 2010;10:670–82.
125. McDonald ES, Randon KR, Knight A, Windebank AJ. Cisplatin preferentially binds to DNA in dorsal root ganglion neurons in vitro and in vivo: a potential mechanism for neurotoxicity. Neurobiol Dis. 2005;18:305–13.
126. Mendonca LM, da Silva MC, Teixeira CC, de Freitas LA, Bianchi Mde L, Antunes LM. Curcumin reduces cisplatin-induced neurotoxicity in NGF-differentiated PC12 cells. Neurotoxicology. 2013;34:205–11.
127. Siddik ZH. Cisplatin: mode of cytotoxic action and molecular basis of resistance. Oncogene. 2003;22:7265–79.
128. Agthong S, Kaewsema A, Charoensub T. Curcumin ameliorates functional and structural abnormalities in cisplatin-induced neuropathy. Exp Neurobiol. 2015;24:139–45.
129. Al Moundhri MS, Al-Salam S, Al Mahrouqee A, Beegam S, Ali BH. The effect of curcumin on oxaliplatin and cisplatin neurotoxicity in rats: some behavioral, biochemical, and histopathological studies. J Med Toxicol. 2013;9:25–33.
130. Kumar P, Barua CC, Sulakhiya K, Sharma RK. Curcumin ameliorates cisplatin-induced nephrotoxicity and potentiates its

anticancer activity in SD rats: potential role of curcumin in breast cancer chemotherapy. Front Pharmacol. 2017;8:132.
131. Kawashiri T, Inoue M, Mori K, et al. Preclinical and clinical evidence of therapeutic agents for paclitaxel-induced peripheral neuropathy. Int J Mol Sci. 2021;22:8733.
132. Hajialyani M, Hosein Farzaei M, Echeverria J, Nabavi SM, Uriarte E, Sobarzo-Sanchez E. Hesperidin as a neuroprotective agent: a review of animal and clinical evidence. Molecules. 2019;24:648.
133. Semis HS, Kandemir FM, Kaynar O, Dogan T, Arikan SM. The protective effects of hesperidin against paclitaxel-induced peripheral neuropathy in rats. Life Sci. 2021;287:120104.
134. Shapiro H. Could n-3 polyunsaturated fatty acids reduce pathological pain by direct actions on the nervous system? Prostaglandins Leukot Essent Fatty Acids. 2003;68:219–24.
135. Mazza M, Pomponi M, Janiri L, Bria P, Mazza S. Omega-3 fatty acids and antioxidants in neurological and psychiatric diseases: an overview. Prog Neuropsychopharmacol Biol Psychiatry. 2007;31:12–26.
136. Ghoreishi Z, Esfahani A, Djazayeri A, et al. Omega-3 fatty acids are protective against paclitaxel-induced peripheral neuropathy: a randomized double-blind placebo controlled trial. BMC Cancer. 2012;12:355.
137. de Aguiar Pastore SJ, de Souza Fabre ME, Waitzberg DL. Omega-3 supplements for patients in chemotherapy and/or radiotherapy: a systematic review. Clin Nutr. 2015;34:359–66.
138. Liu YW, Liu CT, Su YL, Tsai MY. A narrative review of complementary nutritional supplements for chemotherapy-induced peripheral neuropathy. Altern Ther Health Med. 2020;26:43–9.
139. Das J, Ghosh J, Manna P, Sil PC. Taurine protects rat testes against doxorubicin-induced oxidative stress as well as p53, Fas and caspase 12-mediated apoptosis. Amino Acids. 2012;42:1839–55.
140. Chowdhury S, Sinha K, Banerjee S, Sil PC. Taurine protects cisplatin induced cardiotoxicity by modulating inflammatory and endoplasmic reticulum stress responses. BioFactors. 2016;42:647–64.
141. Kato T, Tsunekawa M, Wang S, Yamashita T, Ma N. Effect of taurine on iNOS-mediated DNA damage in drug-induced renal injury. Adv Exp Med Biol. 2017;975(Pt 2):717–27.
142. Owoeye O, Adedara IA, Farombi EO. Pretreatment with taurine prevented brain injury and exploratory behaviour associated with administration of anticancer drug cisplatin in rats. Biomed Pharmacother. 2018;102:375–84.
143. Tsai SJ, Kuo WW, Liu WH, Yin MC. Antioxidative and anti-inflammatory protection from carnosine in the striatum of MPTP-treated mice. J Agric Food Chem. 2010;58:11510–6.
144. Yehia R, Saleh S, El Abhar H, Saad AS, Schaalan M. L-Carnosine protects against Oxaliplatin-induced peripheral neuropathy in colorectal cancer patients: a perspective on targeting Nrf-2 and NF-kappaB pathways. Toxicol Appl Pharmacol. 2019;365:41–50.
145. Tsutsumi K, Kaname T, Shiraishi H, Kawashiri T, Egashira N. Polaprezinc reduces paclitaxel-induced peripheral neuropathy in rats without affecting anti-tumor activity. J Pharmacol Sci. 2016;131:146–9.
146. Majsterek I, Gloc E, Blasiak J, Reiter RJ. A comparison of the action of amifostine and melatonin on DNA-damaging effects and apoptosis induced by idarubicin in normal and cancer cells. J Pineal Res. 2005;38:254–63.
147. Pereira AF, Lino JA, Alves BWF, et al. Amifostine protects from the peripheral sensory neuropathy induced by oxaliplatin in mice. Braz J Med Biol Res. 2020;53:e10263.
148. De Vos FY, Bos AM, Schaapveld M, et al. A randomized phase II study of paclitaxel with carboplatin +/- amifostine as first line treatment in advanced ovarian carcinoma. Gynecol Oncol. 2005;97:60–7.
149. Lorusso D, Ferrandina G, Greggi S, et al. Phase III multicenter randomized trial of amifostine as cytoprotectant in first-line chemotherapy in ovarian cancer patients. Ann Oncol. 2003;14:1086–93.
150. Hilpert F, Stahle A, Tome O, et al. Neuroprotection with amifostine in the first-line treatment of advanced ovarian cancer with carboplatin/paclitaxel-based chemotherapy–a double-blind, placebo-controlled, randomized phase II study from the Arbeitsgemeinschaft Gynakologische Onkologoie (AGO) Ovarian Cancer Study Group. Support Care Cancer. 2005;13:797–805.
151. Duval M, Daniel SJ. Meta-analysis of the efficacy of amifostine in the prevention of cisplatin ototoxicity. J Otolaryngol Head Neck Surg. 2012;41:309–15.
152. Koukourakis MI, Simopoulos C, Minopoulos G, et al. Amifostine before chemotherapy: improved tolerance profile of the subcutaneous over the intravenous route. Clin Cancer Res. 2003;9:3288–93.
153. Salat K. Chemotherapy-induced peripheral neuropathy-part 2: focus on the prevention of oxaliplatin-induced neurotoxicity. Pharmacol Rep. 2020;72:508–27.
154. Karlsson JO, Kurz T, Flechsig S, Nasstrom J, Andersson RG. Superior therapeutic index of calmangafodipir in comparison to mangafodipir as a chemotherapy adjunct. Transl Oncol. 2012;5:492–502.
155. Glimelius B, Manojlovic N, Pfeiffer P, et al. Persistent prevention of oxaliplatin-induced peripheral neuropathy using calmangafodipir (PledOx((R))): a placebo-controlled randomised phase II study (PLIANT). Acta Oncol. 2018;57:393–402.
156. Canta A, Chiorazzi A, Pozzi E, et al. Calmangafodipir reduces sensory alterations and prevents intraepidermal nerve fibers loss in a mouse model of oxaliplatin induced peripheral neurotoxicity. Antioxidants (Basel). 2020;9:594.
157. Karlsson JO, Ignarro LJ, Lundstrom I, Jynge P, Almen T. Calmangafodipir [Ca4Mn(DPDP)5], mangafodipir (MnDPDP) and MnPLED with special reference to their SOD mimetic and therapeutic properties. Drug Discov Today. 2015;20:411–21.
158. Karlsson JOG, Jynge P, Ignarro LJ. The damaging outcome of the POLAR phase III trials was due to avoidable time-dependent redox interaction between oxaliplatin and PledOx. Antioxidants (Basel). 2021;10:1937.
159. Silva VDG, Reis AS, Pinz MP, et al. Further analysis of acute antinociceptive and anti-inflammatory actions of 4-phenylselenyl-7-chloroquinoline in mice. Fundam Clin Pharmacol. 2017;31:513–25.
160. Vogt AG, Voss GT, de Oliveira RL, et al. Organoselenium group is critical for antioxidant activity of 7-chloro-4-phenylselenyl-quinoline. Chem Biol Interact. 2018;282:7–12.
161. Reis AS, Paltian JJ, Domingues WB, et al. Advances in the understanding of oxaliplatin-induced peripheral neuropathy in mice: 7-chloro-4-(phenylselanyl) quinoline as a promising therapeutic agent. Mol Neurobiol. 2020;57:5219–34.
162. Reis AS, Martins CC, da Motta KP, et al. Interface of aging and acute peripheral neuropathy induced by oxaliplatin in mice: target-directed approaches for Na(+), K(+)-ATPase, oxidative stress, and 7-Chloro-4-(phenylselanyl) quinoline therapy. Mol Neurobiol. 2022;59:1766–80.
163. Paltian JJ, Dos Reis AS, Martins AWS, et al. 7-Chloro-4-(phenylselanyl) quinoline is a novel multitarget therapy to combat peripheral neuropathy and comorbidities induced by paclitaxel in mice. Mol Neurobiol. 2022;59:6567–89.
164. Ferrier J, Bayet-Robert M, Dalmann R, et al. Cholinergic neurotransmission in the posterior insular cortex is altered in preclinical models of neuropathic pain: key role of muscarinic M2 receptors in Donepezil-induced antinociception. J Neurosci. 2015;35:16418–30.

165. Selvy M, Mattevi C, Dalbos C, et al. Analgesic and preventive effects of donepezil in animal models of chemotherapy-induced peripheral neuropathy: involvement of spinal muscarinic acetylcholine M2 receptors. Biomed Pharmacother. 2022;149:112915.
166. Kawashiri T, Shimizu S, Shigematsu N, Kobayashi D, Shimazoe T. Donepezil ameliorates oxaliplatin-induced peripheral neuropathy via a neuroprotective effect. J Pharmacol Sci. 2019;140:291–4.
167. Ongnok B, Khuanjing T, Chunchai T, et al. Donepezil protects against doxorubicin-induced chemobrain in rats via attenuation of inflammation and oxidative stress without interfering with doxorubicin efficacy. Neurotherapeutics. 2021;18:2107–25.
168. Kerckhove N, Tougeron D, Lepage C, et al. Efficacy of donepezil for the treatment of oxaliplatin-induced peripheral neuropathy: DONEPEZOX, a protocol of a proof of concept, randomised, triple-blinded and multicentre trial. BMC Cancer. 2022;22:742.