The Effect of Nutraceuticals on Incidence and Severity of Chemotherapy-Induced Peripheral Neuropathy: A Narrative Review

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ABSTRACT

Introduction: Chemotherapy-induced peripheral neuropathy (CIPN) is a common and debilitating side effect of cancer treatments involving platinum and taxane agents such as paclitaxel, cisplatin, and oxaliplatin. This review evaluates the efficacy of three natural health products (NHPs)—omega-3 fatty acids, l-glutamine, and melatonin—on the incidence and severity of CIPN symptoms.

Methods: A search of PubMed was conducted from inception to October 2024. Inclusion criteria were human trials assessing the effect of either omega-3s, l-glutamine or melatonin on the incidence or severity of CIPN as a primary outcome, caused by platinum and taxane chemotherapy, with outcomes measured by clinical evaluations and scoring tools.

Results: Six clinical trials met the inclusion criteria. Of the included studies, three randomized controlled trials (RCTs) examined the effect of omega-3s, one RCT and one non-randomized trial examined l-glutamine, and one open-label pilot trial assessed melatonin. The participants enrolled in the studies did not have CIPN at baseline, with NHP administration starting during chemotherapy with some extending shortly after. Therefore, studies evaluated the effect of the NHPs on the incidence or severity of CIPN symptoms. Supplementation with omega-3 fatty acids and l-glutamine demonstrated statistically significant reductions in the incidence and severity of CIPN across multiple studies involving patients on paclitaxel and oxaliplatin regimens. In a small single-arm pilot study, melatonin use was associated with a lower neuropathy incidence, compared with historical incidence rates.

Discussion: Omega-3 fatty acids and l-glutamine, when used individually, may reduce the incidence and severity of neuropathic pain while supporting nerve function. However, a small number of relevant studies were identified, including small sample sizes and methodological limitations. Future research should include more human trials and further explore supplement safety, efficacy, and underlying mechanisms to establish integrative protocols for reducing the risk and severity of chemotherapy-induced neuropathy in cancer patients.

Key Words CIPN, natural health products, orthomolecular, l-glutamine, omega-3 fatty acids, melatonin

INTRODUCTION

Chemotherapy-induced peripheral neuropathy (CIPN) is a prevalent and often debilitating side effect of various chemotherapeutic agents, particularly platinum compounds (e.g., cisplatin, oxaliplatin) and taxanes (e.g., paclitaxel, docetaxel).[1] The symptoms include sensory disturbances, such as numbness, tingling, and burning pain.[1,2] In severe cases, CIPN can also affect motor function and balance, significantly impairing quality of life and leading to chemotherapy dose reductions or discontinuation.[1] CIPN is a dose-limiting toxicity, as its development can necessitate treatment delays, dose reductions, or discontinuation, which can compromise the overall effectiveness of cancer therapy.[1] The mechanisms underlying CIPN are multifactorial and include direct neuronal toxicity, mitochondrial dysfunction, oxidative stress, and inflammation targeting the dorsal root ganglia and peripheral nerves.[2] It is estimated that 30% of patients have peripheral neuropathy a year or more after finishing chemotherapy.[1]

To mitigate symptoms of peripheral neuropathy, several neuromodulatory agents such as calcium-magnesium infusions, antiepileptic drugs like carbamazepine and gabapentin, amifostine, and glutathione have demonstrated some activity in the prophylaxis and treatment of oxaliplatin-induced acute neuropathy.[2]

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Duloxetine is commonly used off-label in oncology settings because it has been shown to reduce neuropathic pain intensity and improve quality of life in patients who already have CIPN. CIPN treatment is an off-label indication for duloxetine; however, it has not been shown to reduce the incidence or severity of neuropathy in patients undergoing chemotherapy who do not yet have symptoms.[3] Despite its high incidence, there are currently no Health Canada-approved agents for the prevention of CIPN, highlighting the need for safe and effective therapeutic options.[4] There are ongoing studies that are looking into the prevention and efficacy potential of pharmaceutical drugs.[5,6]

L-glutamine is an abundant amino acid in the human plasma and skeletal muscle and serves key metabolic and physiological functions in the body.[7] Although considered conditionally essential, its demand increases substantially under stress conditions, including cancer and chemotherapy. Glutamine is a primary energy substrate for rapidly proliferating cells, particularly enterocytes and immune cells, and supports protein synthesis, nitrogen transport, and glutathione production involved in cellular antioxidant defense.[6] In oncology care, glutamine depletion can contribute to gut mucosal atrophy, immune suppression, and treatment-related toxicity.[7] As such, glutamine supplementation has been investigated for its potential neuroprotective properties in CIPN, with proposed mechanisms including enhanced neuronal energy metabolism and protection from oxidative stress.[7] It may reduce oxidative stress by supporting glutathione synthesis and modulating inflammation through cytokine regulation.[8] Additionally, l-glutamine has been shown to preserve the structure and function of peripheral nerves by mitigating axonal damage and supporting neuronal regeneration.[8]

Omega-3 polyunsaturated fatty acids (PUFAs), primarily eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are essential fats known for their potent anti-inflammatory and neuroprotective properties. Found abundantly in fish, omega-3s modulate the production of pro-inflammatory cytokines and are known to influence membrane fluidity and neuronal signalling.[9] In the setting of CIPN, omega-3s may attenuate neuronal damage by stabilizing nerve membranes, reducing neuroinflammation, and downregulating pathways that are implicated in neuropathic pain.[9] Oxaliplatin-induced nerve injury is driven by mitochondrial dysfunction, oxidative stress, neuroinflammation, and disruptions in neuronal membrane integrity. Omega-3s help counter these processes by incorporating into neuronal cell membranes to improve membrane stability and fluidity, reducing the production of pro-inflammatory cytokines, and supporting mitochondrial energy metabolism.[10] They also enhance the generation of specialized pro-resolving mediators that actively downregulate inflammatory signalling implicated in neuropathic pain.[10]

Melatonin is an endogenously produced hormone synthesized by the pineal gland, best known for regulating circadian rhythms and promoting sleep. Beyond its chronobiotic effects, melatonin possesses robust antioxidant and anti-inflammatory properties, making it a compelling candidate for neuroprotection.[11] It readily crosses the blood-brain barrier and has been shown to scavenge reactive oxygen species (ROS), inhibit nitric oxide production, and modulate pro-inflammatory cytokine release. In the context of CIPN, melatonin may protect peripheral nerves from oxidative and inflammatory damage induced by chemotherapeutic agents, particularly taxanes.[11]

The purpose of this review is to evaluate the efficacy of l-glutamine, melatonin and omega-3 fatty acids on the incidence and severity of CIPN in patients receiving platinum- or taxane-based agents. While several published studies have explored a wide range of NHP interventions for CIPN, this narrative review focuses specifically on these three NHPs and their clinical impact in these commonly used chemotherapy classes.[12,13,14]

METHODS

A literature search was conducted to identify relevant clinical studies evaluating the effects of omega-3 fatty acids, glutamine, and melatonin on the incidence and severity of CIPN. Databases searched included PubMed to identify clinical studies evaluating the efficacy of identified NHPs on the incidence or severity of CIPN. Participants in the included studies did not have CIPN at baseline. In this review, we selected omega-3s, glutamine, and melatonin as the interventions of interest because, after preliminary searching, they were deemed to have limited safety risk and preliminary clinical evidence in CIPN management.

Boolean operators (AND/OR) were used to combine keywords related to CIPN, specific chemotherapeutic agents (e.g., paclitaxel, oxaliplatin), and interventions (e.g., omega-3, glutamine, melatonin). Additional articles were identified via manual review of reference lists in eligible studies and relevant reviews. Data search was conducted in November 2024, with no restrictions based on the date of publication. Studies were included in this review if they met the following criteria:

1. Published in English in a peer-reviewed journal.
2. Conducted with human participants undergoing chemotherapy with either taxane- or platinum-based agents.
3. Evaluated the effects of omega-3 fatty acids, l-glutamine, or melatonin (any route of administration)
4. Incidence or severity of peripheral neuropathy was a primary outcome.
5. Employed validated clinical tools for evaluating neuropathy incidence or severity, such as reduced Total Neuropathy Score (rTNS), National Cancer Institute Common.
6. Clinical trials of any design.

All studies that met these criteria are included in the present review.

Studies were excluded if they were non-clinical in nature, including animal models, in vitro research, or narrative reviews. Observational studies, case reports, editorials, or studies not directly evaluating CIPN incidence or severity as a primary outcome were also omitted. Studies that involved other chemotherapy agents besides taxane- and platinum-based drugs were excluded. However, in colon cancer, oxaliplatin is generally not used as monotherapy, so studies involving chemotherapy for colon cancer include oxaliplatin in combination with capecitabine.

Studies were screened independently, in duplicate. Extracted data were analyzed qualitatively to assess for trends, patterns and gaps. A formal risk of bias assessment was not conducted.

RESULTS

A total of 94 studies were found in initial database searches. After applying the inclusion and exclusion criteria, 6 studies were included in the final analysis (see Table 1).

Three RCTs assessed the impact of omega-3 fatty acids on CIPN. A double-blind RCT involved 57 female participants with breast cancer, on paclitaxel chemotherapy, who were supplemented with either 640 mg of omega-3 fatty acid capsules (54% DHA, 10% EPA) or a placebo of sunflower oil soft gelatin capsules three times daily during chemotherapy, and for 1 month at the end of therapy.[9] 70% of patients (21/30) did not develop CIPN in the omega-3 fatty acids supplemented group, while 40.7% (11/27) did not develop CIPN in the placebo group. This was statistically significant with a *p* value of 0.029. In terms of severity, 13.3% of patients (4/30) developed mild peripheral neuropathy, 16.7% (5/30) developed moderate peripheral neuropathy, and 0% developed severe peripheral neuropathy in the omega-3 group. In the placebo group, 37% (10/27) developed mild peripheral neuropathy, 18.5% (n=5/27) developed moderate peripheral neuropathy, and 3.7% (1/27) developed severe peripheral neuropathy. There was no statistically significant difference in the severity of peripheral neuropathy between groups (p=0.054).[9] A double-blind RCT involving 71 patients, male and female, with stage 3 colon cancer, on oxaliplatin and capecitabine chemotherapy, were supplemented with either 640 mg of omega-3 fatty acid capsules (54% DHA, 10% EPA) or a placebo of sunflower oil capsules three times daily during chemotherapy, and for 1 month after the end of therapy.[10] 47% of patients (17/36) did not develop CIPN while supplemented with omega-3 fatty acids. In contrast, 11% of patients (4/35) in the placebo group did not develop CIPN. This difference is statistically significant, with a *p* value of 0.002. In terms of the severity of CIPN developed, in the omega-3 group, mild peripheral neuropathy was seen in 42% of patients, moderate in 3% and severe in 8%. In the placebo group, mild peripheral neuropathy was seen in 57% of patients, moderate in 20% and severe in 12%. The difference in severity of CIPN is statistically significant between groups, with a *p* value of 0.001.[10] A double-blind RCT involving 179 patients, male and female, with stage 3 or 4 colon cancer, on oxaliplatin combined with capecitabine, were supplemented with either 640 mg of omega-3 PUFAs (54% DHA, 10% EPA) or placebo capsules, three times a day during chemotherapy, and for 1 month after the end of therapy.[15] When supplemented with omega-3 fatty acids, 47.8% of patients (43/90) did not develop peripheral neuropathy. When supplemented with placebo, 30.3% of patients (27/89) did not develop peripheral neuropathy. In terms of severity, 27.8% (25/90) developed stage 1, 12.2% (11/90) developed stage 2, 6.7% (6/90) developed stage 3 and 5.6% (5/90) developed stage 4 peripheral neuropathy, when supplemented with omega-3 PUFAs. In the placebo group, 24.7% (22/89) developed stage 1, 12.4% (11/90) developed stage 2, 19.1% (17/90) developed stage 3, and 13.5% (12/90) developed stage 4 peripheral neuropathy. The difference in both incidence and severity between groups is statistically significant, with both *p* values of 0.017. There was also a significant difference in quality-of-life scores in the omega-3 PUFA group compared with the placebo group (p=0.046), and an increase in appetite loss in the placebo group (p=0.025).[15]

One RCT and one non-randomized study assessed the impact of l-glutamine supplementation on CIPN. An RCT included 86 participants with colorectal cancer undergoing chemotherapy with oxaliplatin.[7] Participants were randomized to obtain or not obtain 15 g of l-glutamine twice daily for 7 consecutive days every 2 weeks, beginning on the day of chemotherapy infusion. When supplemented with 15 g twice daily of l-glutamine, compared with the placebo, a lower percentage of grade 1–2 peripheral neuropathy was observed in the l-glutamine group (16.7% vs 38.6%, p=0.04) after two cycles of oxaliplatin treatment, and a significantly lower incidence of grade 3–4 neuropathy was noted in the l-glutamine group after four cycles (4.8% vs 18.2%, p=0.05) and six cycles (11.9% vs 31.8%, p=0.04). Additionally, interference with daily activities due to neuropathy was reported by 16.7% of patients in the l-glutamine group, compared with 40.9% in the control group (p=0.017). Oxaliplatin dose reductions due to neuropathy were necessary in 7.1% of patients in the l-glutamine group, compared with 27.3% in the control group (p=0.024).[7] In a non-randomized unblinded study, 46 patients with breast cancer on high-dose paclitaxel chemotherapy were given either 10 g of l-glutamine, three times daily, for 4 days, starting 24 hours after beginning paclitaxel treatment (n=17) or no l-glutamine supplementation (n=29).[16] L-glutamine supplementation caused significant changes in weakness, vibratory sensation and toe numbness parameters. Patients who received l-glutamine experienced significantly less weakness compared with those in the control group (p=0.02). The l-glutamine group had a significantly lower incidence of vibratory sensation loss compared with the control group (p=0.04). Lastly, patients receiving l-glutamine reported significantly less toe numbness than those who did not receive l-glutamine (p=0.004).[16]

One study assessed the impact of melatonin supplementation on CIPN. In a non-controlled, open-label, phase 2 pilot trial, 22 participants with breast cancer being treated with either paclitaxel or docetaxel were enrolled. Patients were supplemented with 21 mg of melatonin every day for the duration of taxane chemotherapy and for 28 days following completion of treatment. When supplemented with melatonin, 45% of patients (10/22) developed neuropathy. This included 23% with grade 1 neuropathy and 22% with grade 2 neuropathy; no patients developed grade 3 neuropathy. 55% of patients (12/22) reported no neuropathy. The median score on the FACT-Taxane quality-of-life assessment remained stable, with only a 0.5-point median decline from baseline to the end of the study, suggesting that melatonin did not adversely affect quality of life. The authors note a historical incidence rate of CIPN around 60%. Although this study found a lower incidence rate, given the small and uncontrolled nature, no conclusion can be drawn.[11]

Safety reporting across the included studies was limited. The melatonin study reported on serious adverse effects, which seem to

TABLE 1 Studies included in the narrative review

Authors	Sample Size and Study Design	Interventions	Comparison	Outcome Measures	Results
Ghoreishi et al., 2012	N=57 Randomized double blind placebo-controlled trial	Participants received omega-3 fatty acid capsules, 640 mg 3 times daily (totaling 1,920 mg per day), during chemotherapy and for 1 month after completing paclitaxel treatment.	Participants received placebo capsules following the same schedule.	Evaluate the presence and severity of paclitaxel-induced peripheral neuropathy based on rTNS score	**Incidence:** The study found that 70% of patients in the omega-3 group did not develop peripheral neuropathy, compared with 40.7% in the placebo group. This difference was statistically significant (p=0.029). **Severity:** There was no statistically significant difference in PN severity between the groups.
Esfahani et al., 2016	N=71 Randomized double-blind placebo-controlled trial	Patients received 640 mg of omega-3 fatty acids 3 times daily (totaling 1,920 mg per day) during chemotherapy and for 1 month after completing oxaliplatin and capecitabine treatment.	Patients received placebo capsules following the same schedule.	Incidence of oxaliplatin-induced peripheral neuropathy based on rTNS	**Incidence:** 47% of patients in the omega-3 group did not develop CIPN, compared with 11% of patients in the placebo group. This difference was statistically significant (p=0.002). **Severity:** The severity of neuropathy, assessed using the rTNS, was significantly lower in the omega-3 group compared with the placebo group (p=0.001).
Zhang et al., 2020	N=179 Double-blind RCT	Patients received 640 mg of omega-3 fatty acids 3 times daily (totaling 1,920 mg per day) during chemotherapy and for 1 month after completing oxaliplatin and capecitabine treatment.	Patients received placebo capsules following the same schedule.	Nerve conduction studies measured with a Nicolet/ VIASYS Viking Quest EMG Machine	**Incidence:** 47.8% of patients did not develop PN when supplemented with omega-3 fatty acids. 30.3% of patients did not develop PN in placebo group. This difference is statistically significant (p=0.017). **Severity:** The severity of neuropathy was significantly lower in the omega-3 group compared with placebo (p=0.017).
Wang et al., 2007	N=86 Pilot study	Patients received 15 g of oral glutamine twice daily (totaling 30 g per day) for 7 consecutive days, starting on the day of each oxaliplatin infusion.	Participants did not receive glutamine supplement.	Incidence and severity of oxaliplatin-induced peripheral neuropathy using NCI-CTC–based sensory neuropathy grades	**Incidence:** A lower percentage of grade 1–2 peripheral neuropathy was observed in the l-glutamine group (16.7% vs 38.6%, p=0.04) after 2 cycles of oxaliplatin treatment, and a significantly lower incidence of grade 3–4 neuropathy was noted in the l-glutamine group after 4 cycles (4.8% vs 18.2%, p=0.05) and 6 cycles (11.9% vs 31.8%, p=0.04). **Impact on Daily Activities**: Interference with daily activities due to neuropathy was reported by 16.7% of patients in the glutamine group, compared with 40.9% in the control group. (p=0.017). **Oxaliplatin Dose Reduction:** Dose reductions due to neuropathy were necessary in 7.1% of patients in the glutamine group, compared with 27.3% in the control group (p=0.024).
Stubblefield et al., 2005	N=46 Non-randomized study	Participants received 10 g of glutamine 3 times daily for 4 days starting 24 hours after completing paclitaxel treatment.	Participants did not receive glutamine supplement.	Severity of paclitaxel-induced peripheral neuropathy using clinical neurologic examination and patient-reported symptoms	**Weakness:** Patients who received glutamine experienced significantly less weakness compared with those in the control group (p=0.02). **Loss of Vibratory Sensation:** The glutamine group had a significantly lower incidence of vibratory sensation loss compared with the control group (p=0.04). **Toe Numbness:** Patients receiving glutamine reported significantly less toe numbness than those who did not receive glutamine (p=0.004).
Nahleh et al., 2010	N=22 Open-label, phase II pilot clinical trial	All participants received 21 mg of melatonin daily at bedtime throughout their taxane chemotherapy regimen and continued for an additional 28 days post-chemotherapy.	This was a single-arm study without a placebo or control group. The outcomes were compared with historical data on the incidence of taxane-induced neuropathy.	Incidence and severity of taxane-induced PN using NCI-CTC as well as neuropathy grade	**Incidence of Neuropathy:** 45% of patients (10 out of 22) developed neuropathy: Grade 1: 23% (5 patients) Grade 2: 23% (5 patients) No cases of Grade 3 or higher neuropathy were reported. **No Neuropathy:** 55% of patients (12 out of 22) did not experience any neuropathy. **Quality of Life:** The median score on the FACT-Taxane quality-of-life assessment remained stable, with only a 0.5-point median decline from baseline to the end of the study, suggesting that melatonin did not adversely affect quality of life.

rTNS = reduced total neuropathy score; NCI-CTC = National Cancer Institute common toxicity criteria; PN = peripheral neuropathy; CIPN = chemotherapy-induced peripheral neuropathy; FACT = functional assessment of cancer therapy.

be attributed to the chemotherapy treatment itself. This included grade 3 nausea/vomiting (n=3) and grade 3 fatigue (n=1). Adverse effects plausibly attributed to melatonin include mild nighttime sedation in two individuals, with no daytime sedation reported.[11] One of the included l-glutamine studies reported that all patients completed 6 cycles of chemotherapy, and glutamine supplementation did not adversely affect treatment response or survival, with similar chemotherapy response rates and comparable median survival times between groups. Additionally, no significant differences were observed in non-neurologic toxicities, including grade 3–4 leukopenia, thrombocytopenia, and hepatic or renal function impairment (p=0.76), indicating that oral glutamine was well tolerated.[7] No other studies reported safety outcomes of the agents used, commented on impacts on chemotherapy effectiveness or evaluated long-term efficacy beyond the active chemotherapy period.

DISCUSSION

Supplementation with omega-3 fatty acids and l-glutamine demonstrated statistically significant reductions in the incidence and severity of CIPN across multiple RCTs involving patients on paclitaxel and oxaliplatin regimens, while data for melatonin is too preliminary for reliable interpretation.

The three omega-3 RCTs included patients receiving either paclitaxel for breast cancer or oxaliplatin-based regimens for colorectal cancer, indicating that effects may extend across major neurotoxic chemotherapies. All studies used an omega-3 dose of 640 mg 3 times daily, which is a relatively low dose compared with the 2–4 g/day commonly used in clinical practice, potentially limiting the magnitude of observed effects. Across the studies, omega-3 supplementation reduced the proportion of patients developing CIPN and, in the oxaliplatin trials, reduced severity and improved quality-of-life scores. However, 2 of the oxaliplatin studies shared similar sample sizes, dosing, follow-up periods, and study protocols, raising the possibility of overlapping patient populations and limiting the independence of the evidence.[9,10,15]

For l-glutamine, evidence comes from one RCT in oxaliplatin-treated colorectal cancer patients and one non-randomized study in high-dose paclitaxel-treated breast cancer patients. The RCT demonstrated reductions in CIPN incidence and severity, decreased interference with daily activities and fewer chemotherapy dose reductions. The non-randomized, unblinded trial focused on specific signs and symptoms of CIPN, noting that l-glutamine–supplemented patients experienced less lower extremity weakness, loss of vibration and toe numbness. Dosing regimens differed between studies (15 g twice daily for 7 days every 2 weeks versus 10 g three times daily for 4 days per cycle) as well as study design, making direct comparisons challenging. Sample sizes were modest, and follow-up was limited to the active chemotherapy period, leaving long-term outcomes and optimal dosing unclear.[7,16]

The evidence for melatonin is limited. A single small, single-arm pilot study reported that over half the participants did not develop neuropathy; however, without a control group, no conclusions can be drawn regarding efficacy.[11]

Possible Mechanism of Action

Several proposed mechanisms might mediate the impact of omega-3 fatty acids on CIPN, particularly through their influence on neuronal structure, function, and inflammatory signaling. Omega-3 fatty acids integrate into neuronal cell membranes, influencing signal transduction, ion transport, receptor function, and neurotransmission. Omega-3-fatty acids, particularly DHA, help reduce neuropathic pain by directly modulating nerve activity and inhibiting proinflammatory cytokines such as IL-1β, IL-6 and TNF-α.[17] Neuroprotectin D1 (NPD1) is created from DHA, and is a neuroprotective agent. NDP1 promotes axonal regeneration and reduces expression of pro-inflammatory cytokines.[9,10,14] Omega-3 fatty acids also prevent the slowing down of nerve conduction velocity, through improving Na+/K+ ATPase activity.[9,10] Mice enriched with genes that increase omega-3 fatty acids have exhibited a greater recovery to peripheral nerve injury and reduced neuronal cell death.[17] Omega-3 fatty acid metabolites have also been shown to promote neuronal growth and function.[17] DHA contributes to greater flexibility and fluidity in cell membranes, which could allow for faster production of synaptic vesicles that deliver neurotransmitters, therefore enhancing neuronal signaling.[18] RCTs have shown that patients supplemented with omega-3 fatty acids during taxane- or platinum-based chemotherapy experienced significantly lower incidence and severity of peripheral neuropathy compared with placebo groups.[9,10] These promising outcomes suggest omega-3 supplementation may serve as a safe and effective intervention in reducing the risk and severity of CIPN and improve chemotherapy tolerance.

The mechanism of neuroprotection by l-glutamine is unclear, yet research suggests it may offer neuroprotection by upregulating nerve growth factor (NGF), which declines as neuropathy worsens. NGF administration prevents paclitaxel-induced neuropathy in mice, and l-glutamine has been shown to increase NGF mRNA in animal models.[8] Additionally, high systemic l-glutamine may reduce glutamate conversion, potentially contributing to symptom relief.[16] A common fear with l-glutamine supplementation is that it will protect tumour cells from the cytotoxic effects of chemotherapy.[7] However, several studies have refuted this claim since there were no between-group differences in chemotherapy response rates.[7,16] Some studies have shown an increased immune response with l-glutamine supplementation, hence decreased tumour growth.[16]

Melatonin may provide neuroprotection during chemotherapy through multiple mechanisms, including reducing oxidative stress, regulating mitochondrial function, and suppressing the formation of free radicals that contribute to neurotoxicity.[11] In addition to its potential role in CIPN, melatonin is widely used in oncology supportive care due to its demonstrated effects on improving treatment tolerance. Research has shown that melatonin supplementation is associated with lower rates of thrombocytopenia, malaise, asthenia, stomatitis, and cancer-related cachexia, collectively supporting improved quality of life during chemotherapy.[19] Importantly, melatonin does not appear

to interfere with the antitumour efficacy of chemotherapy agents, as clinical data have shown no reduction in response rates among patients receiving melatonin as an adjunct therapy.[11] These findings suggest that melatonin may offer a safe and biologically plausible strategy to reduce chemotherapy-related toxicities, including neuropathy.

Strengths and Limitations

A notable strength of this review is its narrowed focus on three specific NHPs, which allowed for a more detailed exploration of the evidence and proposed mechanisms of action, compared with broader reviews that evaluate broader topics. In addition, we developed a priority eligibility criterion in order to minimize selection bias.

Several limitations of this review and the available literature should be considered when interpreting the findings. First, a key limitation of this paper is its narrative review format, which lacks the methodological rigour and comprehensive search strategy of a systematic review. Second, the literature search was conducted using a single database. This raises the possibility that relevant studies may have been missed, and the findings may not fully represent the complete body of evidence on NHPs for CIPN. Third, no formal risk of bias assessment was performed to evaluate the quality of the included studies. As a result, confidence in the reported findings is limited, and methodological shortcomings in the original studies may have influenced the results. Fourth, there is a lack of human trials investigating NHPs for CIPN. Additionally, there is a lack of quality studies among those available. Many of the included studies have a small sample size, and had design flaws such as a lack of randomization or blinding, or the absence of a control or placebo group. Fifth, the studies mentioned a lack of long-term follow-up. Because of this, the influence of these NHPs on chemotherapy efficacy, survival outcomes, and sustained neuroprotective effects for CIPN remains unclear. While the available studies did not indicate any negative impact on chemotherapy dosing or response, formal assessment of long-term treatment outcomes was not performed, highlighting the need for future trials to evaluate both neuropathy prevention and potential interactions with antineoplastic therapy over time. Sixth, there was minimal reporting in the included studies on direct safety or adverse effects of the interventions themselves, limiting conclusions about their tolerability. Seventh, given the small body of evidence on this topic, there is a small number of studies included. The studies included involved patients receiving treatment for several different types of cancer with limited overlap. Furthermore, as the included studies primarily involved patients with breast and colorectal cancers, the findings may not be generalizable to other cancer types treated with taxane- or platinum-based chemotherapy. While CIPN is largely driven by the neurotoxic mechanisms of these agents rather than the underlying malignancy, variations in chemotherapy protocols, dosing schedules, and patient characteristics across cancer types may influence outcomes. Therefore, extrapolation of these results to other oncology populations should be made with caution. Lastly, we acknowledge that the included trials utilized different neuropathy assessment scales and chemotherapy regimens, which may have contributed to variability in the reported outcomes.

Further Research

While current evidence is promising, several limitations in the literature highlight important directions for future research to strengthen the clinical application of nutraceutical use in CIPN. These include higher-quality studies, with larger sample sizes and longer follow-up. Further studies can include research on the mechanism of action of these NHPs to more deeply understand their neuroprotective potential. Additionally, trials comparing these products to one another using the same study methods would allow for accurate comparison, permitting the establishment of the superiority of one therapy. A greater number of well-designed melatonin studies could also allow for a comprehensive understanding of its effectiveness and mechanism of action. Future studies are warranted to investigate NHPs across similar cancer types to strengthen comparability and clinical relevance as well. Beyond individual efficacy, these NHPs may offer additive or synergistic effects when used in combination, given their distinct neuroprotective mechanisms. Omega-3 fatty acids reduce neuroinflammation and modulate ion channels, l-glutamine supports neuronal regeneration and nerve growth factor expression, and melatonin scavenges free radicals and protects against oxidative injury. No current clinical trials have investigated combined supplementation; however, future research should explore multi-agent protocols to determine whether concurrent use provides superior protection against CIPN. Another key consideration is the variability in trial design across studies reviewed, including differences in sample sizes, dosages, treatment durations, and outcome measures, which limits direct comparison and generalizability. While these supplements are generally safe, accessible, and cost-effective, especially compared with pharmacologic agents like duloxetine, their integration into standard oncology practice faces challenges due to regulatory limitations and a lack of widespread education in integrative care. Patient-reported outcomes such as functional impairment, pain interference, and quality of life also remain underreported and should be prioritized in future trials. Including more outcome measures in further research, such as CIPN incidence, severity, and specific nerve conduction parameters, would allow for a more holistic view of the NHPs' effect.

Additionally, longer-term follow-up data are lacking, which impairs our understanding of whether these agents merely delay neuropathy onset or offer lasting neuroprotection post-chemotherapy. Future research should include more large-scale randomized human trials and further explore NHP safety, efficacy, and underlying mechanisms. Expanding research in these areas will help solidify the role of NHPs in reducing the incidence and severity of CIPN and support the development of evidence-based integrative protocols.

Clinical Application

Omega-3 fatty acids and l-glutamine show promise for reducing the incidence and severity of CIPN in patients undergoing

platinum- and/or taxane-based chemotherapy. CIPN can be a debilitating adverse effect that may necessitate a reduction in chemotherapy dose or early discontinuation. One RCT assessing l-glutamine demonstrated a lower incidence of required oxaliplatin dose reductions due to CIPN in the l-glutamine group compared with control.[7] However, this finding is limited to a single study, and long-term safety data were not assessed. Current evidence remains insufficient to conclude that supplementation with l-glutamine or omega-3 fatty acids reliably prevents chemotherapy dose reductions or interruptions. Larger, more robust clinical trials with long-term safety monitoring are required before making definitive clinical recommendations or conclusions regarding long-term outcomes.

CONCLUSION

Omega-3 fatty acids and l-glutamine, when used individually, may reduce the severity and incidence of chemotherapy-induced neuropathic pain, while supporting nerve function. Future human studies with greater sample sizes and rigorous study designs can allow for a more comprehensive analysis of these NHPs, holding the potential for the development of integrative protocols to address CIPN. Expanding available CIPN management tools has the potential to improve patient outcomes by enhancing the efficacy and tolerability of chemotherapy.

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CONFLICTS OF INTEREST DISCLOSURE

We have read and understood the *CAND Journal*'s policy on conflicts of interest and declare that we have none.

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