Published in final edited form as:

Crit Rev Oncol Hematol. 2016 February ; 98: 325–334. doi:10.1016/j.critrevonc.2015.11.014.

Natural Products and Complementary Therapies for Chemotherapy-Induced Peripheral Neuropathy: A Systematic Review

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Abstract

Chemotherapy-induced peripheral neuropathy (CIPN) is a serious dose-limiting side-effect without any FDA-approved treatment option. Prior reviews focus mostly on pharmacological interventions, but nonpharmaceutical interventions have also been evaluated. A Web of Science and PubMed database search to identify relevant RCTs from January 2005 to May 2015 included the terms: CIPN, cancer; *and* supplements, vitamin E, goshajinkigan, kampo, acetyl-L-carnitine, carnitine, alpha-lipoic acid, omega-3, glutamine, *or* glutamate; *or* massage, acupuncture, mind-body practice, yoga, meditation, Tai-Chi, physical activity, *or* exercise. Of 1465 publications screened, 12 RCTs evaluated natural products and one evaluated electroacupuncture. Vitamin E may help prevent CIPN. L-glutamine, goshajinkigan, and omega-3 are also promising. Acetyl-L-carnitine may worsen CIPN and alpha-lipoic acid activity is unknown. Electroacupuncture was not superior to placebo. No RCTs were published regarding other complementary therapies, although some studies mention positive incidental findings. Natural products and complementary therapies deserve further investigation, given the lack of effective CIPN interventions.

Keywords

chemotherapy; peripheral neuropathy; platinum drugs; natural products; dietary supplements; complementary therapies; integrative medicine; randomized controlled trials

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Conflict of interest

The authors have no conflicts of interest.

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1. Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is a frequent dose-limiting side effect for cancer patients treated with platinum-derived compounds, vinca alkaloids, taxanes, and the proteasome inhibitor bortezomib [1]. Neurotoxicity incidence varies depending on the agent used and cumulative dose [2], with rates ranging from 19% to more than 85% in patients treated with multiple agents [3, 4]. A recent meta-analysis showed a CIPN prevalence of 68.1% (95% CI = 57.7–78.4) within the first month post-chemotherapy, 60.0% at 3 months, and 30.0% at 6 months or later. Even with significant heterogeneity among studies, this analysis confirmed that the high prevalence of CIPN in cancer patients has a significant negative impact on long-term quality of life (QoL) [5].

CIPN presents most often as sensory polyneuropathy, manifesting as paresthesia, pain, or burning sensations [6]. Motor deficits occur less frequently than sensory deficits and can include generalized muscle weakness [6]. Recovery may take months or even years. The mechanisms are usually attributed to microtubule disruption (taxanes, vinca alkaloids) or a direct toxic effect (platinums) [7]. In some cases, symptoms are severe enough to require chemotherapy dose reductions [6–8], resulting in reduced chemotherapeutic benefit for patients [9, 10]. In other cases, symptoms decrease QoL by affecting mobility and limiting ability to perform simple daily activities [7, 11]. For oxaliplatin-induced neuropathy, the symptoms of acute neuropathy that occur in approximately 90% of patients reverse within a week [12]. Chronic neuropathy, however, persists in significant proportions of patients for a year or even longer after chemotherapy cessation [13–15]. It has been shown that oxaliplatin-induced neuropathy reduced QoL if cancer patients received a cumulative dose 842 mg/m² and scored higher on EORTC QLQ-CIPN20 sensory scale problems compared with those who received a low cumulative dose of <421 mg/m² (mean 19 vs. 8; $p = 0.02$) [12, 16]. For paclitaxel-treated patients, more than 50% of patients who received a cumulative dose >250 mg/m² (26% of the targeted cumulative dose) reported paresthesia or hyperalgesia, and most of these patients experienced sensory or sensory and autonomic neuropathy [17]. As a result of severe CIPN, about 8% of breast and 12% of colorectal cancer patients require chemotherapy dose reductions or treatment discontinuation altogether, with devastating effects on treatment efficacy and survival [13, 18].

Currently there is no consistent evidence from double-blind randomized controlled trials (RCTs) of any drug's efficacy to prevent these challenging side effects. The effectiveness of drugs used to treat other types of neuropathy may not extend to CIPN, as in the case of the tricyclic antidepressant amitriptyline [19, 20], gabapentin [21], opioids [22], or other interventions such as calcium and magnesium infusion [23, 24]. The only successful CIPN trial showed that the antidepressant duloxetine at 30 mg daily for 1 week followed by 60 mg daily for 4 more weeks produced a modest 1.06 point reduction in pain on a 10-point scale from baseline (vs. 0.34, placebo), but was also associated with fatigue and nausea and a 12% dropout rate (vs. 1%, placebo) [25]. Several complementary medicine modalities including natural products available as dietary supplements have been investigated for the prevention and treatment of CIPN, although only a few studies have been properly conducted.

Integrative oncology addresses symptoms associated with cancer and cancer treatment using evidence-based non-invasive therapies that are adjuncts to mainstream therapy. These modalities are clearly distinguished from alternative therapies that forego mainstream treatment and lack scientific evidence of safety and efficacy [26]. The Society of Integrative Oncology Guidelines [27] have categorized the range of complementary therapies to include: dietary supplements (which include many natural products), acupuncture, touch therapy, mind-body modalities, and physical activity. These interventions have become significant resources in the arena of cancer care, owing to their high usage prevalence among patients during active oncology treatment and throughout survivorship [28, 29].

To date, a comprehensive systematic review of RCTs of natural products and complementary therapies to manage CIPN in cancer care has not been conducted. The goal of this article is to provide healthcare practitioners and patients with an unbiased review of the best evidence currently available on these treatments for CIPN management.

2. Design

We searched the Web of Science and PubMed Central databases for relevant prospective RCTs related to natural products and complementary therapies for CIPN published from January 2005–May 2015. The search algorithm used medical subject heading terms and/or keywords frequently used in complementary medicine articles: (((chemotherapy-induced peripheral neuropathy) OR (CIPN) OR (peripheral neuropathy AND cancer)) with ((supplements) OR (vitamin E) OR (goshajinkigan) OR (kampo) OR (acetyl-L-carnitine) OR (carnitine) OR (alpha-lipoic acid) OR (omega-3) OR (glutamine) OR (glutamate)) OR ((complementary therapy) OR ((massage) OR (touch therapy)) OR (acupuncture) OR ((mind-body practice) OR (yoga) OR (meditation) OR (Tai-Chi)) OR ((physical activity) OR (exercise)))). Studies were further restricted to prospective RCTs, English language, and integrative oncology modalities in CIPN prevention or cure. Meta-analyses, case reports, unpublished reports, letters to the editor, retrospective chart reviews, and interim data analyses were excluded (Fig. 1). We did not include animal model-based studies because applicability and generalizability to human populations has not been established. The lead author independently read and selected from all retrieved references and abstracts. Search criteria categories aligned with the aforementioned Society of Integrative Oncology Guidelines [27] categories of integrative therapies and are discussed herein as natural products, acupuncture, touch therapy, mind-body modalities, or physical activity.

3. Results

A total of 1465 publications were screened, from which 13 RCTs were identified. Over half were published in the past 4 years (Table 1), suggesting an increased interest in natural products and complementary therapies to address CIPN.

3.1 Natural product studies

3.1.1 Vitamin E—An essential nutrient that functions as a lipid soluble antioxidant, Vitamin E is found in vegetable oils, nuts, and green leafy vegetables. The compound alpha-tocopherol demonstrates the highest vitamin E activity. RRR-alpha-tocopherol is the natural

form available in plants, while the more commonly used form is synthetic all-rac-alpha-tocopheryl acetate. Tocopherols are absorbed in the small intestine as free alcohols alone or in combination with emulsified fat product and transported to the liver to be metabolized. Nutritional deficiency of vitamin E is rare. Genetic defects for alpha-tocopherol transfer protein lead to severe deficiency with neurological disorders.

Argyriou et al [30] evaluated prophylactic vitamin E to prevent cisplatin-induced peripheral neuropathy (CPN). The treatment group received oral alpha-tocopherol 300 mg twice daily during cisplatin chemotherapy and for up to 3 months afterwards while the control group did not. The primary endpoint was neurotoxicity incidence based on Neurological Symptom Score (NSS) and Neurological Disability Score (NDS), performed after cycle 3, cycle 6, and 3 months post-chemotherapy. Between-group differences for neurotoxicity incidence were significant, with relative risk (RR) for its development significantly higher in the control than treatment group, suggesting vitamin E may prevent cisplatin neurotoxicity.

Argyriou et al [31] also assessed synthetic dl-alpha-tocopheryl acetate 300 mg twice daily for paclitaxel-induced PN (PPN) versus non-supplemented controls. In addition to NSS and NDS scales, the Hughes' Functional Grading Scale (FGS) was used to assess functional ability. Neurotoxicity incidence also differed significantly between supplementation and control groups, with RR for developing PPN significantly higher for control participants. In addition, FGS assessments indicated that supplemented participants were largely unaffected versus controls. Along with protective effects, supplementation was also safe and well tolerated.

The neuroprotective role of prophylactic vitamin E for CPN was confirmed in a phase III RCT by Pace et al [32]. Patients receiving cisplatin were randomly assigned to begin oral alpha-tocopherol 400 mg/day or placebo (rice powder) before starting chemotherapy, and continue until 3 months post-chemotherapy. However, only 41 patients receiving cumulative cisplatin doses $>300 \text{ mg/m}^2$ were eligible for statistical analysis. Neurotoxicity incidence and symptom severity as measured by Total Neuropathy Score (TNS) was significantly lower with alpha-tocopherol than placebo.

Contrary to the above-mentioned studies, a phase III double-blind RCT by Kottschade et al [33] did not find significant benefit with Vitamin E. Enrolled patients with various cancers received either dl-alpha-tocopherol 400 mg twice daily or placebo, starting within 4 days of the first chemotherapy cycle and continuing through 1 month post-chemotherapy. The primary endpoint was incidence of grade 2 sensory neuropathy (SN) as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v3.0. Cytotoxic agents included taxanes, cisplatin, carboplatin, oxaliplatin, or combination therapy. Investigators found no difference in grade 2 SN incidence between the two arms, although supplementation was well tolerated.

An explanation for the contrasting results may be that Kottschade et al [33] used a different evaluation scale and patients received various chemotherapeutic drugs. Platinum compounds such as cisplatin and oxaliplatin share similarities in their neurotoxicity by interacting with DNA and adding platinum deposits in the dorsal root ganglion responsible for apoptosis in

sensory neurons. However it's also known that differences occur according to their chemical structure and pharmacokinetic property [43]. For example, even if oxaliplatin produced less platinum-DNA adducts compared with cisplatin, it appears to be more aggressive due to its ability to escape DNA repair systems.

An RCT by Afonseca et al [34] evaluating alpha-tocopherol for prevention of oxaliplatin-induced PN (OPN) supports these differences between oxaliplatin and cisplatin. Colorectal and gastric cancer patients were randomized to receive either alpha-tocopherol 400 mg daily or placebo starting 5 days before chemotherapy and until the end of treatment. There were no significant between-group differences in reduction of grade 1/2 PN according to the NCI-CTCAEv3.0 scale.

3.1.2 Glutamate and glutamine—Preliminary animal studies suggest that glutamine may prevent neurotoxicity caused by administration of vincristine, paclitaxel, or cisplatin [44]. Glutamine is the most abundant non-essential amino acid in blood and constitutes 60% of the total free amino acid pool in skeletal muscles. It contains two amine groups per molecule, playing an important role as a nitrogen transporter and providing precursor nitrogen for the synthesis of purines and pyrimidines [45]. Glutamine is depleted in stress states such as major surgery, sepsis, and cancer. In most tissues, there is either glutamate production from glutamine (by glutaminase), or glutamine production from glutamate (by glutamine synthetase). L-glutamate is intracellular and cannot readily traverse the cell membrane, and when supplied as a supplement, needs amino acid transporters to enter cells. Enterocytes play a major role in glutamine metabolism.

The most recent multicenter double-blind RCT by Loven et al [36] included electrodiagnostic evaluations to assess whether glutamate could help to prevent PPN. Patients received either glutamate 500 mg three times daily or placebo capsules throughout six cycles of paclitaxel and carboplatin and for 3 weeks after. Patients were evaluated by neurological examinations, questionnaires (severity scores, SS), and sensory–motor nerve conduction studies. The primary objective was to determine the portion of patients who completed six chemotherapy cycles without clinically significant PPN, defined either by the rate of patients with signs and symptoms corresponding to SS 2–3, or by the rate of apparent impaired electrophysiological features. There were no significant between-group differences in symptom frequency although neurotoxicity symptoms presented mostly with lower SS in the glutamate group. This study suggests that glutamate supplementation at the chosen dosage regimen fails to protect against PPN.

Oral glutamine was evaluated for preventing OPN in a pilot study by Wang et al [35]. Metastatic colorectal cancer patients were randomized to usual care plus glutamine 15 g twice daily for 7 consecutive days every 2 weeks beginning the day of oxaliplatin infusion or to usual care alone. Effects on chemotherapy efficacy, neurological toxicity (NCI-CTCAEv2.0), and electrophysiological alterations were assessed. A significantly lower percentage of grade 1/2 PN was observed in the glutamine versus usual care group after two treatment cycles, with significantly lower incidences of grade 3/4 neuropathy after four and six cycles. There were no significant between-group differences in chemotherapy efficacy, electrophysiological abnormalities, grade 3/4 non-neurological toxicities, or survival. These

data indicate that oral glutamine significantly reduces OPN incidence and severity without affecting chemotherapy response and survival.

3.1.3 Goshajinkigan—Kampo medicine, based on traditional Chinese medicine as practiced in Japan, employs the use of goshajinkigan, an herbal formula composed of ten natural ingredients and purported to affect sensory nerves. It has recently been considered as a treatment for taxane neuropathy [46] and diabetic neuropathy [47].

An RCT by Nishioka et al [37] of colorectal cancer patients suggested that goshajinkigan 7.5 g/day significantly reduced grade 3 neuropathy incidence (primary endpoint) in the goshajinkigan versus control group after 10 cycles of modified folinic acid-fluorouracil-oxaliplatin-6. Neuropathy was evaluated during every course according to the Neurotoxicity Criteria of Debiopharm. Other sensory neuromodulatory agents such as calcium–magnesium infusions or antiepileptic-like agents were not allowed.

Kono et al [38] also evaluated goshajinkigan for colorectal cancer patients in a double-blind RCT. Participants received oral goshajinkigan 7.5 g/day or placebo powder for 26 weeks, beginning with their initial FOLFOX infusion. The primary endpoint was incidence of grade 2 OPN after 8 cycles. CIPN severity was assessed according to NCI-CTCAEv3.0 at baseline, every 2 weeks until cycle 8, and every 4 weeks thereafter until week 26. By cycle 8, grade 2 OPN incidence in the goshajinkigan versus placebo group was 39% and 51% respectively and grade 3 OPN incidence was 7% and 13% respectively, but neither was significant. Subanalyses by chemotherapy type and secondary endpoints including chemotherapy response rate also indicated no significance differences, suggesting that goshajinkigan is at least not worse than placebo for OPN. It should be noted that investigator goals were to obtain a more accurate sample size estimate as well as confirm that goshajinkigan had a similar toxicity to placebo before further evaluation of its potential to prevent progression and development of severe OPN.

3.1.4 Acetyl-L-carnitine—Acetyl-L-carnitine is an ester of the trimethylated amino acid L-carnitine that is synthesized in the human brain, liver, and kidneys by the enzyme acetyl-L-carnitine-transferase and plays an essential role in intermediary metabolism. In mitochondria, it ensures the availability of acetyl-CoA for the elimination of toxic metabolic products, and is involved in acetylation of different proteins including tubulin that play a role in neuronal protection. Most of the studies concerning acetyl-L-carnitine have been done for diabetic [48, 49] or human immunodeficiency virus (HIV) patients [50, 51].

A double-blind RCT by Hershman et al [39] compared efficacy of oral acetyl-L-carnitine 3,000 mg daily for 24 weeks with a cellulose placebo capsule in women undergoing adjuvant taxane-based chemotherapy. CIPN prevention as the primary endpoint was measured using the 11-item neurotoxicity component of the Functional Assessment of Cancer Therapy-Neurotoxicity/Taxane (FACT-NTX) scale at 12 weeks. Secondary objectives included changes in 12- and 24-week endpoints, functional status (FACT-Trial Outcome Index [TOI]), fatigue (Functional Assessment of Chronic Illness Therapy [FACIT]-Fatigue), and NCI-CTCAEv3.0 motor and sensory NTX grade. At week 12, FACT-NTX scores were 0.9 points lower with acetyl-L-carnitine than placebo indicating

more CIPN, whereas week 24 scores were 1.8 points lower with acetyl-L-carnitine. Serum carnitine levels increased with acetyl-L-carnitine but remained stable with placebo. Despite evidence from preclinical and phase II studies indicating that acetyl-L-carnitine may be effective for both treatment and prevention of taxane-induced PN symptoms, investigators in this large RCT found no evidence of CIPN prevention at 12 weeks (the primary endpoint), and that acetyl-L-carnitine actually increased CIPN and decreased functional status at 24 weeks. Supplementation resulted in an increase in serum carnitine in the acetyl-L-carnitine arm, with no change in the placebo group over time, and no between-group differences in treatment delays or chemotherapy dose reductions.

3.1.5 Alpha-lipoic acid—As an essential cofactor in energy production, alpha-lipoic acid acts as a potent antioxidant, and exerts apoptotic effects on tumor cell lines [52-54]. Dihydrolipoic acid is a reduced form of lipoic acid. In human studies, alpha-lipoic acid improved insulin sensitivity, vasodilation, and polyneuropathy in patients with diabetes mellitus [55]. However, only one RCT evaluated whether alpha-lipoic acid could prevent neuropathy from platinum-based chemotherapy.

In Guo et al [40], patients were randomized to oral alpha-lipoic acid 1,800 mg daily or placebo for 24 weeks except during the period between 2 days before and 4 days after each dose of platinum to avoid potentially compromising chemotherapy efficacy. Whether alpha-lipoic acid could prevent CIPN was measured by the 11-item Gynecologic Oncologic Group-Neurotoxicity component of FACT at week 24. Only 70 patients completed the study due to change of regimens, non-compliance, missing data, or unknown reasons. No between-group statistical differences were found.

3.1.6 Omega-3 fatty acids—Omega-3 fatty acids such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are polyunsaturated fatty acids incorporated into the phospholipid membrane of cells including those of the central and peripheral nervous systems. Omega-3 fatty acids have cardioprotective, anti-inflammatory, and immunomodulatory effects due to their ease of assimilation by plaque lipids which improve atherosclerotic plaque stability [56], and their ability to reduce IL-6 levels [57, 58].

Ghoreishi et al [41] evaluated omega-3 fatty acid supplementation for PPN in breast cancer patients in a double-blind RCT. Participants were randomized to receive either omega-3 fatty acids 640 mg (DHA-54%; EPA-10%) three times daily or placebo throughout paclitaxel chemotherapy and for 1 month after. PPN existence and severity was measured as the primary outcome 1 month post-chemotherapy by reduced TNS. A significant between-group difference was observed for PN incidence, with a 70% lower risk in the omega-3 fatty acid group. Although this study is small, it does suggest that prophylactic omega-3 fatty acids may be an efficient neuroprotective agent.

3.2 Complementary therapy studies

3.2.1 Acupuncture studies—Acupuncture has been part of Traditional Chinese Medicine for more than 2,000 years. Since the 1997 National Institutes of Health consensus [59] declared acupuncture a complementary intervention and with numerous clinical and neuroscience studies published in recent years, this modality has become more accepted in

the West. Acupuncture has been associated with a number of biochemical mediators including 5-hydroxytryptamine, glutamate, adenosine and beta-endorphin [60], and has been investigated to treat HIV- [61, 62] and diabetes-associated [63, 64] PN.

Only one RCT has evaluated acupuncture for CIPN. In this four-arm study, Rostock et al [42] evaluated the effectiveness of electroacupuncture (EA, ~8 sessions) compared with hydroelectric bath (~8 sessions), daily vitamin B, or daily placebo capsules in 60 patients over a 3-week period, with additional follow-up at 12 weeks. Although no significant between-group differences were observed, baseline complaints of CIPN were unexpectedly low, especially in the EA group, while study design including sample size calculations was based on expectations of more severe CIPN symptoms. Therefore, a floor effect with narrow margins by which to measure improvement may explain these negative results that contrast with other preliminary data.

In a nonrandomized controlled trial by Schroeder et al [65], nerve conduction studies were used to evaluate acupuncture for 10 weeks plus best medical care (BMC) versus BMC only in patients with various cancer types and chemotherapy regimens. Intervention patients received a standard 10-week treatment of ST34, the five extra points EX–LE12 (at the tip of the toes), and the four extra points EX–LE8 (at the web of the toes). Needles were inserted bilaterally for 20 minutes. A ± 2 m/s change in sural nerve conduction velocity (NCV) from initial assessments was considered significant. In five of six patients treated with acupuncture, mean NCV significantly improved after 6 months. In another pilot study by Bao et al [66], 27 multiple myeloma patients with moderate to severe bortezomib-induced peripheral neuropathy experienced significantly reduced neuropathic pain and improved functioning following 10 weeks of acupuncture treatment (twice weekly for 2 weeks, once weekly for 4 weeks, and then biweekly for 4 weeks). Another single-arm study by Garcia et al [67] demonstrated that electroacupuncture was safe and possibly effective in treating thalidomide/bortezomib-induced peripheral neuropathy in 19 multiple myeloma patients with significant improvements in Functional Assessment of Cancer therapy-neurotoxicity score after 9 weeks treatment. The intervention was conducted over a 9-week period of 20 acupuncture sessions at 2–3 times weekly.

3.2.2 Touch Therapy Studies—The medical literature on massage therapy for neuropathy is scant, with no RCTs. Only one case report [68] describes effleurage and petrissage techniques applied to the extremities of a 45-year-old patient with grade 2 CIPN resulting from docetaxel and cisplatin treatment for stage IV esophageal adenocarcinoma. After CIPN in all extremities for approximately 8 months (6 months post-chemotherapy), the patient received 3 sessions weekly of manual therapy over 6 weeks by two licensed massage therapists. Superficial cutaneous temperature was monitored using infrared thermistry as a proxy for microvascular blood flow. Significant increases in superficial temperature of the fingers and toes were observed, suggesting symptom improvement. At the conclusion of manual therapy and with no change in medications, CIPN symptoms were greatly reduced to grade 1 as measured by the MD Anderson Symptom Inventory with corresponding improvement in QoL. Further studies are warranted.

3.2.3 Mind-Body Practice—With these key words, no articles on meditation, yoga, or other mind-body practices for CIPN were found. However, self-management strategies to reduce CIPN symptoms have included yoga and mindfulness [69], indicating these patient-centered approaches may be worthy of evaluation.

3.2.4 Physical Activity—Motor impairments and functional limitations caused by CIPN lead to postural instability and altered locomotion biomechanics, which raise the risk for falls. Therefore, whether prescribed physical activity could reduce the effects of CIPN would be particularly valuable, but are lacking in the clinical literature. A large prospective study by Mols et al [70] was conducted among a population-based sample of colorectal cancer survivors up to 11 years post-diagnosis to evaluate previously suspected inverse relationships between exercise and CIPN [71] [72]. Among 1648 patients surveyed, investigators found that not meeting the Dutch physical activity guidelines of 150 minutes of moderate to vigorous physical activity weekly was significantly associated with CIPN-like symptoms among those not treated with chemotherapy as well as more CIPN among the 506 patients treated with chemotherapy.

Although a recent RCT by Henke et al [73] evaluated a specified strength and endurance training in patients with stage IIIA–IV lung cancer during palliative platinum-based chemotherapy, this study was not designed with any primary measure of CIPN reduction in mind. Rather, secondary measures that included a single score for PN from the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ) Core-30 identified a significant difference in this measure among other parameters that indicated enhanced physical activity during palliative chemotherapy is helpful. However, the mode of exercise bears particular mention as hallway and stair walking exercises were used in addition to resistance-band strength training. Recent guidelines [74] indicate that for patients with PN who have stability issues, stationary biking or water aerobics rather than walking be considered if stability is affected, and to monitor discomfort in hands, using padded gloves for cycling or other activities as required.

4. Discussion

CIPN has a wide-reaching impact across various cancer patient populations. Neuropathic pain is highly prevalent in long-term survivors of breast [75], ovarian, and germ cell cancers [76]. Currently, no effective reliable treatment has been established to prevent or treat CIPN symptoms. Duloxetine has only modest results with associated side effects and a high dropout rate [25]. The 2014 American Society of Clinical Oncology CIPN guidelines moderately recommend treatment with duloxetine, with further research in this area [77]. New safe and effective treatments are clearly needed.

Increased interest in CIPN has included the investigation of several nonpharmaceutical interventions. To the best of our knowledge, this is the first systematic review of the literature base for both natural health products and complementary therapies to prevent and manage CIPN in cancer care.

Most studies were done using dietary supplements and showed mixed results. To date, five RCTs examine the effects of vitamin E in CIPN prevention, with three suggesting a preventative effect and two that did not. Mechanisms underlying CIPN pathogenesis differ according to the chemotherapy agent used, which may explain conflicting results for CPN versus PPN [32, 33] L-glutamine did not appear to protect against PPN [36] but may help to prevent OPN without reducing chemotherapy efficacy [35]. The herbal formula goshajinkigan [37, 38] and omega-3 fatty acids [41] appear active in preventing OPN and PPN, respectively, although whether or not they would compromise chemotherapy efficacy was not tested. Acetyl-L-carnitine may worsen CIPN when given during chemotherapy [39] despite positive phase II trial results, and one study on alpha-lipoic acid found no prevention benefit, although data from less than one-third of patients were used [40].

Whether physical activity can induce reductions in CIPN has not been directly evaluated in RCTs and would be a worthwhile primary endpoint for future study designs based on positive secondary findings [73], cancer population-based studies [70], and reported self-management strategies that include physical exercise, yoga, and mindfulness [69]. Indeed, the fact that patients are willing to adopt these behavior-based interventions to manage CIPN symptoms, and that there are positive incidental findings for these modalities as well as massage should be clinical impetus to research their value with respect to CIPN. In the evidence base across these therapies, their unique but related contributions to improvement in pain management and QoL as well as physical and emotional conditioning are well established, and this may likely extend to benefits in reduction of CIPN. Acupuncture may also be effective, but a current lack of RCTs with positive results exists for this endpoint. An ongoing pilot study by Kim et al [78] will be the first multicenter randomized patient-assessor-blinded trial to evaluate electroacupuncture versus sham acupuncture for CIPN using EORTC-QLQCIPN20.

Several limitations limit the ability to draw firm conclusions. First, with respect to our search methodology, limitations include the reading and selection of studies and study details by the lead author only, possible language selection bias with only English language articles selected, no search for unpublished papers or “gray literature” which carries the potential for positive publication bias, the filter of only specific and applicable key words known within integrative oncology categories, and the lack of more explicit bias analysis for each individual study.

Second, among the publications meeting our criteria, objectives across trials were different, with some focusing on CIPN prevention at first delivery of chemotherapy, and others evaluating interventions as treatment of established CIPN. Most studies were designed to evaluate the efficacy of an intervention in CIPN prevention. Lack of long term follow-up for outcomes measured is also a limitation, and the use of different evaluation scales and types of chemotherapeutic agents are major limitations. In routine practice, CIPN is evaluated using clinical and instrumental parameters. Usually, objective assessment of neuropathic symptoms is performed using bedside clinical examination in association with toxicity scales. The NCI-CTCAEv3.0 scale appeared to be quick to use and easy to administer, but inter-observer disagreement is frequent [19]. Scoring neurotoxicity by NCT-CTCAE is based on whether symptoms interfere with function (grade 2), activity of daily life (grade 3),

or cause permanent functional impairment or paralysis (grade 4). Even if the NCI-CTCAE scale seems to correlate with the Visual Analog Scale, it does not correlate with the consequences of impairment caused by neuropathic symptoms. In a recent study, neurotoxicity was graded severe (grade 3) in only every third patient who rated neuropathy as the most troublesome symptom [79]. TNS, a composite scale that includes symptoms, signs, ability aspects and electrophysiological measures appears to be more responsive to changes in CIPN severity [80]. Only Pace et al [32] evaluating alpha-tocopherol and Ghoreishi et al [41] evaluating omega-3 fatty acids used TNS scoring. Both CTCAE and TNS scales are most commonly, although not exclusively, used in clinical trials.

Another interesting point is that new diagnostic techniques are being developed to detect early nerve damage. In the near future, it may be possible to determine reliable biomarkers that promptly identify patients at high risk of CIPN. For example, polymorphisms of corresponding cytochrome P450 enzymes could influence paclitaxel clearance and drug-related side effects. Therefore, genotyping may identify cancer patients at risk of developing neurotoxicity so as to advise them on neuroprotectant supplementation before the onset of painful and disabling CIPN [81].

Adequate CIPN management enables patients to tolerate more vigorous cancer treatment, leading to better clinical outcomes. Continued investigation of prognostic factors, early neuropathy biomarkers, more sensitive diagnostics, new drugs, and other neuroprotective strategies are vital. Until reliable and effective interventions are established, the natural health product and complementary interventions described herein deserve more rigorous investigation to ascertain their effectiveness against CIPN without compromising chemotherapy efficacy.

5. Conclusion

Based on the RCTs to date, vitamin E, L-glutamine, goshajinkigan, and omega-3 fatty acids may be effective in preventing CIPN, with varying demonstrated levels of efficacy. On the other hand, these findings are not likely to change clinical practice, as the majority of studies have small sample sizes and some trials evaluating the same supplement have conflicting results. Of equal importance, acetyl-L-carnitine may worsen CIPN when given during chemotherapy. The future landscape of study design for integrative modalities including acupuncture, massage, mind-body therapy, or physical activity particularly needs further seeding in the area of CIPN. Given positive preliminary findings, CIPN prevention or reduction as a primary endpoint in future RCTs examining these modalities is warranted.

Acknowledgments

We thank Barrie Cassileth, PhD, Founding Chief of the Integrative Medicine Service at Memorial Sloan Kettering Cancer Center and members of Reims University of Medicine, especially Hervé Curé, MD, PhD in charge of the oncology resident and fellowship training program and Olivier Bouché, MD, PhD, head of digestive oncology. We also thank François Goldwasser, MD, PhD, and head of the oncology department at Cochin Hospital in Paris. The cooperative exchange among these colleagues in France and the United States contributed to the medical training of young oncologists.

Ingrid Haviland provided writing and editing support in the preparation and submission of this manuscript.

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Abbreviation Glossary

ALA	alpha-lipoic acid
ALC	acetyl-L-carnitine
BMC	best medical care
CIPN	chemotherapy-induced peripheral neuropathy
CPN	cisplatin-induced peripheral neuropathy
DHA	docosahexaenoic acid
EPA	eicosapentaenoic acid
FACIT	Functional Assessment of Chronic Illness Therapy

FACT- TOI	Functional Assessment of Cancer Therapy Trial Outcome Index
FACT-NTX	Functional Assessment of Cancer Therapy-Neurotoxicity/Taxane
FGS	Functional Grading Scale
GJG	goshajinkigan
HIV	human immunodeficiency virus
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCV	nerve conduction velocity
NDS	Neurological Disability Score
NSS	Neurological Symptom Score
O3FA	omega-3 fatty acids
OPN	oxaliplatin-induced peripheral neuropathy
PPN	paclitaxel-induced peripheral neuropathy
QoL	quality of life
RCTs	randomized controlled trials
RR	relative risk
SN	sensory neuropathy
SS	severity scores
TNS	Total Neuropathy Score

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Figure 1.

Records indentified through Web of Science and PubMed Central database searches.

Table 1
RCTs Involving the Use of Natural Products and Complementary Therapies in CIPN Management

Study	RCT Type	Intervention, n	Control, n	CT Regimen	Type of cancer	Endpoints	Results
<i>Vitamin E</i>							
Argyriou et al 2006 [30]	Pilot	Alpha-tocopherol 300 mg bid during + up to 3 mo post CT, 14	Non-supplemented, 16	Cisplatin	Cervix Gastric Head and neck Lung Testicular	NTX incidence based on NSS and NDS after cycle 3, cycle 6, and 3 mo post-CT	NTX incidence: vitamin E, 21.4%; control, 68.5%; $p = 0.026$ CPN RR for control vs suppl, 2.51; 95% CI, 1.16 to 5.47
Argyriou et al 2006 [31]	Pilot	Synthetic dl- α -tocopheryl acetate 300 mg bid during + up to 3 mo post CT, 16	Non-supplemented, 16	Paclitaxel	Breast Lung Ovarian	NTX incidence: NSS/NDS Function/mobility: FGS	NTX incidence: vitamin E, 18.7%; control, 62.5%; $p = 0.03$ PPN RR for control vs suppl group 0.3; 95% CI, 0.1 to 0.9 Function/mobility unaffected in suppl group
Pace et al 2010 [32]	Phase III placebo-controlled	Alpha-tocopherol 400 mg/d, before CT (median 3d) + 3 mo post CT, 17	Rice powder placebo, 24	Cisplatin	Lung Glioblastoma Endometrial Bladder Surrenal gland Carcinoma	Symptom severity using TNS	NTX incidence, vitamin E 5.9%; placebo, 41.7%; $p < 0.01$ mean TNS, 1.4 vs 4.1; $p < 0.01$
Kortschade et al 2011 [33]	Phase III double-blind placebo-controlled	dl-alpha-tocopherol 400 mg bid w/in 4 d of Cycle 1–1 mo post-CT, 96	Placebo, 93	Taxanes Cisplatin Carboplatin Oxaliplatin Combination tx	Breast Lung Other	NCI-CTCAEv3.0 grade 2 sensory neuropathy incidence	No difference in grade 2 SN incidence: vitamin E, 34%; placebo, 29%; $p = 0.43$
Afonseca et al 2013 [34]	Phase II placebo-controlled	Alpha-tocopherol 400 mg/d, 5 days before CT until end of regimen, 18	Placebo, 16	Oxaliplatin	Colorectal Gastric	NCI-CTCAEv3.0 neuropathy incidence	Cumulative incidence: vitamin E, 83%; placebo, 68%; $p = 0.45$
<i>Glutamate/Glutamine</i>							
Wang et al 2007 [35]	Pilot	Glutamine 15 g bid for 7 d q 2 wk + usual care starting CT d1, 42	Usual care alone, 44	Oxaliplatin	Colorectal	CT efficacy, NTX measured by NCI-CTCAEv2.0 and electrophysiological alterations	Gr 1-2 NTX after 2 cycles:*** glutamine, 16.7%; control, 38.6%; $p = 0.04$ Gr 3-4 NTX after 4 cycles: glutamine, 4.8%; control, 18.2%; $p = 0.05$ Gr 3-4 NTX after 6 cycles: glutamine, 11.9%; control, 31.8%; $p = 0.04$ No significant between-group differences for: CT efficacy, electrophysiological abnormalities, grade 3/4 non-neurological

toxicities, or survival.

Loven et al 2009 [36]	Multicenter double- blind placebo- controlled	Glutamate 500 mg tid throughout CT to 3 wks post-CT, 23	Placebo capsule, 20	Paclitaxel + carboplatin	Ovarian	Completion of 6 CT cycles w/o clinically significant PN assessed by neurological exams, severity score questionnaires, and sensory-motor nerve conduction studies	No significant differences, although NTX presented with lower severity in the glutamate group.
Study	RCT Type	Intervention, n	Control, n	CT Regimen	Type of cancer	Endpoints	Results
Goshajinkigan (GJG)							
Nishioka et al 2011 [37]	Pilot	GJG 7.5 g/d throughout CT, 22	Non- supplemented, 23	Oxaliplatin	Colorectal	Significant reduction in DEB-NTC Gr.3 NTX after 10 cycles of mFOLFOX6	Gr 3 neuropathy GJG, 0%; control 12%; $p < 0.01$
Kono et al 2013 [38]	Multicenter double- blind placebo- controlled	GJG 7.5 g/d for 26 wk from CT start, 44	Placebo powder, 45	Oxaliplatin	Colorectal	Grade 2 OPN after 8 cycles measured by NCl-CTCAEv3.0	Nonsignificant positive findings for: Gr 2 CIPN at cycle 8, Gr 3 OPN incidence, and CT response rate
Acetyl-L-carnitine (ALC)							
Hershman et al 2013 [39]	Double- blind placebo- controlled	ALC 3,000 mg/d for 24 wk, 208	Cellulose placebo capsule, 201	Taxanes	Breast	Primary (Wk 12): NTX prevention using FACT-NTX-Taxane scale Secondary (Wk 24): FACT-TOI, FACIT-Fatigue, NCl-CTCAEv3.0 motor/sensory NTX	ALC vs placebo FACT-NTX at Wk 12: ↓0.9 pt (95% CI, -2.2 to 0.4; $p = 0.17$) at Wk 24: ↓1.8 pt (95% CI, -3.2 to -0.4; $p = 0.01$) >5-point decrease more likely (38% v 28%; $p = 0.05$) FACT-TOI at Wk 24: 3.5 points lower ($p = 0.03$) Gr 3-4 NTX: 8 cases vs 1 No between-group differences for: ACIT-Fatigue, CT delays or dose reductions; however, ALC increased NTX and decreased functional status
Alpha-lipoic acid (ALA)							
Guo et al 2014 [40]	Placebo- controlled	ALA 1,800 mg/d for 24 wk except 2d prior-4d post each CT dose, 122	Placebo, 121	Platinums	Breast	NTX prevention using GOG/NTX-FACT at Wk 24	Only 70 patients completed the study (CT regimen changes, noncompliance, missing data, or other) No between-group differences
Study	RCT Type	Intervention, n	Control, n	CT Regimen	Type of cancer	Endpoints	Results
Omega-3 fatty acids (O3FA)							

Ghoreishi et al 2012 [41]	Double-blind placebo-controlled	O3FA 640 mg tid (54% DHA, 10% EPA) during CT+ 1 mo post, 35	Placebo, 34	Paclitaxel	Breast	NTX existence/severity measured by rTNS 1 mo post-CT	O3FA: Reduced PN incidence (OR, 0.3; 95% CI, 0.10 to 0.88; $p = 0.02$) Lowered risk of PN by 70%
Acupuncture							
Rostock et al 2013 [42]	4-arm placebo-controlled	Electroacupuncture, (EA) 14 Acupoints: LV3, SP9, GB41, GB34, LI4, LI11, SI3, and HT3 8 ± 1 EA sessions over 3 weeks	or over 3 weeks: Hydroelectric baths (8 ± 1 sessions), 14 or Vitamin B1/B6 capsules (300/300 mg daily), 15 or Placebo capsules, 17	Taxanes Platinum derivatives Vinca alkaloids	Breast Ovarian Lymphoma Other	Primary: CIPN extent/intensity after Day 21 tx and Day 84 follow-up compared with baseline Secondary: NCI-CTCAEv2.0 EORTC QLQ-C30 at Days 0, 21 and 84	No significant between-group differences; however baseline CIPN complaints were low, esp. in EA group, while sample size calculations were based on more severe symptoms/pain scores

Shaded rows indicate negative studies. No RCTs were published regarding other complementary therapies.

bid, twice daily; **CI**, confidence interval; **CPN**, cisplatin-induced peripheral neuropathy; **CT**, chemotherapy; **DEB-NTC**, Neurotoxicity Criteria of Debiopharm; **EORTC QLQ C-30/LC-13**, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30; **FACIT**, Functional Assessment of Chronic Illness Therapy; **FACT**, Functional Assessment of Cancer Therapy; **FACT-NTX**, FACT-Neurotoxicity/Taxane scale; **FACT-TOI**, FACT Trial Outcome Index; **GOG/NTX**, Gynecologic Oncologic Group-Neurotoxicity; **FGS**, Hughes' Functional Grading Scale; **mFOLFOX6**, modified folinic acid-fluorouracil-oxaliplatin-6; **NCI-CTCAE**, National Cancer Institute Common Terminology Criteria for Adverse Events; **NDS**, Neurological Disability Score; **NSS**, Neurological Symptom Score; **NTX**, neurotoxicity; **OPN**, oxaliplatin-induced PN; **PN**, peripheral neuropathy; **RR**, relative risk; **rTNS**, Reduced Total Neuropathy Score; **tid**, three times daily; **TNS**, Total Neuropathy Score.