REVIEW ARTICLE

Supplemental Preparations in Taxane-Induced Neuropathy Management

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Abstract

Taxane-induced peripheral neuropathy (TIPN) is a dose-limiting adverse effect of chemotherapy without any specific treatment. The aim of this paper is to evaluate the effects of natural products and supplements on TIPN. PubMed, Google Scholar and Web of Science databases were searched through August 2022 regarding TIPN and effects of natural products and supplement therapy. Data consists of preclinical studies, randomized controlled trials and case reports. After screening of 230 papers, we found 13 relevant animal and human studies regarding possible benefits of vitamin E, glutamine, omega-3, acetyl-L-carnitine and group of B vitamins on TIPN. Results demonstrated that vitamin E can be helpful on prevention and duration of TIPN. Glutamine and B vitamins showed hopeful results on reducing pain sensation. Omega-3 also shows promising results on incidence of TIPN. However, acetyl-L-carnitine might develop and worsen neuropathy. Although some supplements revealed promising effects on prevention and treatment of TIPN, researches are still limited and we need further long-term large sample size trials to confirm clinical efficacy of these supplements.

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Keywords: Chemotherapy; Taxane; Peripheral Neuropathy; Supplements

Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is a nerve-damaging side effect of many common chemotherapy drugs. Neuropathy is an important complication of chemotherapy that causes a decrease in the quality of life of cancer survivors, either negative effect on cancer treatment due to the mandatory dose reduction or stopping of some drugs from the treatment regimen. About 30 to 40% of patients will experience CIPN in the course of chemotherapy (1, 2). Among chemotherapy agents, peripheral neuropathy with platinum drugs, taxanes, vinca alkaloids, and bortezomib is more common. Taxanes including paclitaxel, docetaxel, cabazitaxel and nabpaclitaxel belong to the family of antineoplastic drugs classified as microtubule-stabilizing agents. They can be used as a part of chemotherapy regimens for different cancers. They can be used as an option in neoadjuvant, adjuvant or metastatic settings (3, 4).

Incidence of taxane-induced peripheral neuropathy (TIPN) for paclitaxel treatment is 57 to 83% and with docetaxel is 11 to 64%. The incidence of neuropathy with cabazitaxel and nabpaclitaxel is lower than other taxanes. Peripheral neuropathy with cabazitaxel occurs in 13 to 17% of cases and is mostly mild in severity (5-7). The risk of neuropathy depends on multiple factors including the drug itself, cumulative dose , co-administered drugs, comorbidities such as diabetes mellitus, patient age, route of administration and duration of therapy (3). Among these, the most important risk factor is cumulative dose of taxanes. The threshold of cumulative dose of paclitaxel and docetaxel for neuropathy is 1000 mg/m2 and 400 mg/m2, respectively (8). However, neuropathy is even common in lower doses (9, 10). TIPN is bilateral and symmetric and mainly involved in a “stocking and glove” pattern. First numbness occurs in distal of lower extremity. Mostly begins from toes symmetrically and develops ascendingly to involve feet and legs, and also distal of upper extremity and then hands. Pain and paranesthesia are more common in patients with TIPN. However, in severe cases weakness of limbs might occur due to large fiber nerve involvement. Symptoms usually improve or dissolve three to six months after the

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end of treatment, but it may persist in some cases (11, 12). One sign of peripheral nerve damages of taxanes is acute pain syndrome which occurs within 24 hours after the first treatment. The incidence of acute pain syndrome is lower with docetaxel than paclitaxel (47% and 97% respectively) (13, 14).

Management of the TIPN is very challenging because there is not reliable and definite treatment, so we need to evaluate new agents for interventions. Multiple modalities and medications have been used; gabapentin, pregabalin, duloxetine, tricyclic antidepressants, baclofen, opioids, ketamine, and growth factors have been used in neuropathy management. Gabapentin and duloxetine are most common drugs used in TIPN (11, 15, 16). Also, there are some non-pharmacological techniques which are safe and may be beneficial such as exercise, acupuncture and scrambler therapy. None of these interventions proved to be effective in large clinical trials.

On the other hands, some natural products and supplements have been shown hopeful results to improve TIPN in several studies. So, these products might help as additional agent to mitigate taxane-induced neuropathy. In this review, we aim to investigate the effectiveness of these supplements on TIPN.

Methods

This review was conducted by using the PubMed, Google Scholar and Web of Science databases to find relevant studies about TIPN and effects of natural products and supplement therapy. Following keywords were included first: “chemotherapy-induced peripheral neuropathy” OR “CIPN” OR “taxane-induced peripheral neuropathy” OR “TIPN” OR “paclitaxel-induced peripheral neuropathy” OR “docetaxel-induced peripheral neuropathy” AND “supplements” OR “cancer supplements” OR “natural products” OR “biological products”. General related keywords were primarily chosen so that the search results become wide enough not to miss out on any related title. Then the most relevant articles were retrieved among them. Afterwards, a second search was specifically conducted with each yielded supplement name(s). Studies were identified from their inception up to August 2022. No limitation was exerted in the advanced searching.

Results

After screening of 230 papers, we found 13 relevant articles regarding possible benefits of vitamin E, glutamine, glutamate, omega-3, acetyl-L-carnitine and group of B vitamins on TIPN. All these agents are supplement preparations but no natural or herbal products was found to be studied against TIPN alone. Among 13 relevant papers, we found 10 clinical trials (17-26), one case study (27) and two animal studies on rat (28, 29). Herein, details of each study were described according to the supplement that is used. Results also have been summarized in Table 1.

Table 1. Characteristics of the included studies.

Author, Year	Type of study	Chemotherapy regimen	Type of cancer	Sample size	Intervention(s)	Control	Duration	Result(s)	Exclusion criteria
Vahdat et al, 2001	Clinical trial	Paclitaxel (825 mg/m2 over 24 hours single dose)	Breast cancer (Stage 4)	45	Glutamine (10 g t.i.d)	---	During chemotherapy and at least 2 weeks after suspension (mean= 30 days)	Severity and incidence of neuropathy reduced in glutamine group ($P < 0.05$ and $P = 0.04$, respectively).	Central nervous system metastases, compromised organ function, prior progression with taxanes.
Loven et al, 2009	RCT	Paclitaxel (175 mg/ m2 every 3-4 weeks for at least 6 cycles) + carboplatin	Advanced epithelial ovarian cancer or primary peritoneal carcinoma-tosis	43	Glutamate (500 mg t.i.d)	Placebo	During 6 cycles of chemotherapy and 3 weeks after suspension	Glutamate supplementation decreased pain sensation compared to placebo group ($P = 0.011$).	Known neuropathy, diabetes mellitus, history of using drugs known to cause neuropathy.

Table 1. Continued

Author, Year	Type of study	Chemotherapy regimen	Type of cancer	Sample size	Intervention(s)	Control	Duration	Result(s)	Exclusion criteria
Flatters et al, 2006	Animal study (Rat)	Paclitaxel (2mg/kg)	---	---	Acetyl-l-carnitine (50 mg/kg and 100 mg/kg)	Placebo	41 days	Significant different regard to mechanical sensitivity were observed in rats between two groups that showed preventively effect of ACL (P < 00.1). Investigations on established TIPN also showed that ACL can be effective on pain sensation of TIPN (P < 00.5).	---
Badary et al, 2014	RCT	Paclitaxel (135 mg/m2 weekly for 3 cycles)	Breast cancer	40	Acetyl-l-carnitine (1000 mg t.i.d)	Placebo	12 weeks	Incidence of sensory and motor neuropathy significantly reduced in ACL group (P<0.001 and P<0.001, respectively). Also, NGF increased in ACL group unlike control group.	Previously exposed to CIPN, conditions with risk factors for neuropathies, End Stage Renal Disease.
Hershman et al, 2018	RCT	Docetaxel (75 mg/m2 every-three-weeks for 4 or 6 cycles) paclitaxel (80 mg/m2 weekly for 12 cycles or 175 mg/m2 every-two-weeks for 4 cycles or 6 cycles)	Breast cancer (Stage 1-3)	409	Acetyl-l-carnitine (1000 mg t.i.d)	Placebo	2 years	Average difference of NTX-score was significantly different between two groups (P=0.01) and was lower in ACL group. This long-term follow-up showed ACL worsen TIPN and patients are in more risk of complications of TIPN.	Prior history of peripheral neuropathy from other causes, seizure disorder, Patients with history of using vitamin E, glutamine, gabapentin, nortriptyline, amitriptyline, duloxetine HCl or other nutritional supplements to treat CIPN.

Table 1. Continued

Author, Year	Type of study	Chemotherapy regimen	Type of cancer	Sample size	Intervention(s)	Control	Duration	Result(s)	Exclusion criteria
Ghoreishi et al, 2012	RCT	Paclitaxel (175 mg/m2 every three weeks for 4 cycles)	Breast cancer	57	Omega-3 (640 mg t.i.d)	Placebo	During chemotherapy and 1 month after suspension	Incidence of TIPN was statistically significant lower in patients who received omega-3 supplements (P=0.029).	Prior history of chemotherapy treatment, prior neuropathy due to diabetes mellitus, HIV, alcohol abuse, thyroid disfunction, hereditary peripheral neuropathy and take any form of nutritional supplements at least three months before entering the study.
Anoushirvani et al, 2018	RCT	Taxol-based	Solid tumor (lung, breast, ovaries, etc.)	63	Omega-3 (640 mg t.i.d)	Placebo	During chemotherapy and 3 months after suspension	Omega-3 can reduce the incidence of TIPN (P = 0.0001).	Prior history of chemotherapy, prior neuropathy due to diabetes mellitus, AIDS, alcohol abuse, thyroid disfunction, hereditary neuropathy, take any form of nutritional supplements at least three months before entering the study, smoking and drug use, low back pain and the use of other chemotherapy drugs.
Argyriou et al, 2006	RCT	Paclitaxel (175 mg/m2 every-three-weeks for 6 cycles) + carboplatin (or epirubicin)	Solid or non-myeloid tumor	32	Vitamin E (300 mg b.i.d)	---	During chemotherapy and 3 months after suspension	Incidence and severity of neuropathy significantly decrease in vitamin E group (P=0.03, P=0.01 respectively).	Prior history of neuropathy or systemic disease associated with nerve injury and prior history of chemotherapy treatment.
Shamsaei et al, 2017	RCT	Taxol-based	Breast cancer	70	Vitamin E (180 mg b.i.d)	Placebo	During chemotherapy and 3 months after suspension	Vitamin E can prevent sural nerve damage (P=0.007). However, it is ineffective on preventing peroneal and tibial nerve damage (P> 0.05).	History of peripheral neuropathy and systemic diseases (diabetes mellitus, systemic lupus erythematosus, HIV, and alcohol abuse) and patients with prior history of chemotherapy.

Table 1. Continued

Author, Year	Type of study	Chemotherapy regimen	Type of cancer	Sample size	Intervention(s)	Control	Duration	Result(s)	Exclusion criteria
Ali Heiba et al, 2021	RCT	Docetaxel (Median cumulative dose =225 mg/m2) Paclitaxel (Median cumulative dose > 683 mg/m2)	Solid or non-myeloid malignancy	140	Vitamin E (400 mg b.i.d)	---	During chemotherapy and 3 months after suspension	Incidence and onset of neuropathy shows no significant different between two groups (P = 1.0 and P =0.24 respectively). However, results indicated that vitamin E can reduce duration of neuropathy (P = 0.01).	Pre-existing peripheral neuropathy of any cause, kidney or liver disfunction, severe dyspnoea, mental health disabilities, prior history of using chemotherapy agents (Platinums, taxanes or vinca alkaloids), Patients receiving any neuropathic pain medications and pregnant women.
Anoushirvani et al, 2018	RCT	Taxol-based	Solid tumor (lung, breast, ovaries, etc.)	63	Vitamin E (300 mg b.i.d)	Placebo	During chemotherapy and 3 months after suspension	Vitamin E can reduce the incidence of TIPN (P = 0.0001).	Prior history of chemotherapy, prior neuropathy due to diabetes mellitus, AIDS, alcohol abuse, thyroid disfunction, hereditary neuropathy, take any form of nutritional supplements at least three months before entering the study, smoking and drug use, low back pain, the use of other chemotherapy drugs and kidney and liver disfunctions.
Schloss et al, 2016	RCT	Oxaliplatin, Taxanes Vincristine	Tumors	71	Vitamin B complex (50 mg B1, 20 mg B2, 100 mg B3, 163.5 mg B5, 30 mg B6, 500 µg B9, 500 µg B12, 500 µg B7, 100 mg of choline and 500 µg of inositol)	Placebo	36 weeks	B group vitamin showed no significance difference with placebo and could not protect TIPN. Some patients with developed neuropathy in placebo group showed lower blood level of vitamin B12 than base.	Prior history of peripheral neuropathy, previous chemotherapy with a neurotoxic agent, pregnant or breastfeeding, cognitive impairment, alcohol abuse, mental disorder and using nutritional or herbal supplements.

Table 1. Continued

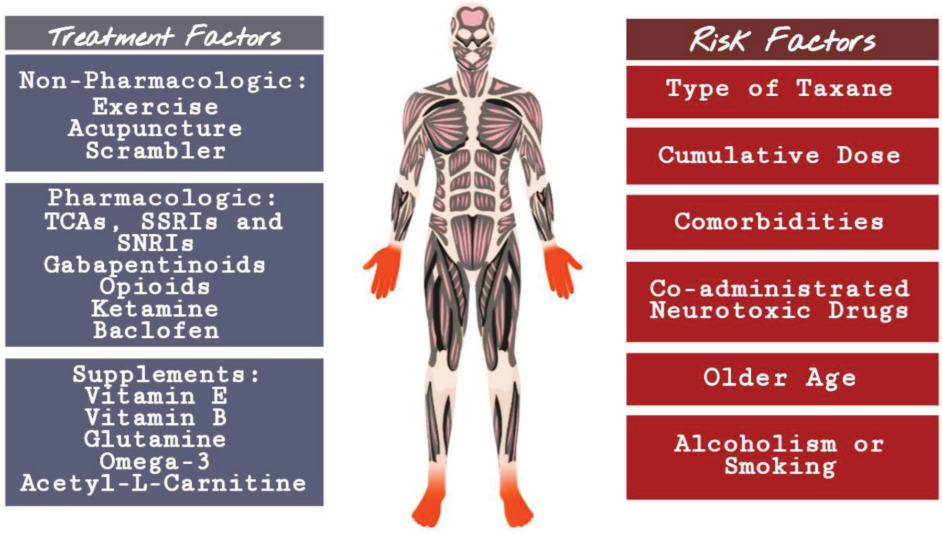
Author, Year	Type of study	Chemotherapy regimen	Type of cancer	Sample size	Intervention(s)	Control	Duration	Result(s)	Exclusion criteria
Hamity et al, 2017	Animal study (Rat)	Paclitaxel (3 intravenous injections of 6.6 mg/kg paclitaxel over 5 days)	---		Vitamin B3 (200 mg/kg/day)	Placebo	7 days before chemotherapy and during chemotherapy and continued for 21 days	Vitamin B3 was effective on prevention of tactile hypersensitivity and blunted place escape–avoidance behaviors (P<0.05).	---
Schloss et al, 2015	Case report	Docetaxel (75 mg/m2) + Cyclophosphamide (600 mg/m2) every-three-weeks for 4 cycles.	Breast cancer		Vitamin B12 + B complex (B complex capsule and 1000 µg IM B12)	Placebo	6 months	After chemotherapy, vitamin B12 blood level decreased comparing to baseline and patient developed grade 2-3 CIPN. Vitamin B12 and B-complex administration resulted to improve CIPN to grade 1.	---

Glutamine

Glutamine is an important non-essential amino acid that stored primarily in skeletal muscle (75%) and liver (25%). Glutamine is naturally found in eggs, beef, white rice, milk, and corn. Among its many functions, glutamine serves as a primary carrier of nitrogen between tissues and is the main energy source for rapidly proliferating cells such as activated lymphocytes and fibroblasts. It is also essential for maintenance of intestinal epithelium for patients on total parenteral nutrition as its omission hastens villous atrophy. Glutamine is depleted in stress states such as major surgery, sepsis, and cancer. (30, 31).

In a study, 12 patients with stage 4 breast cancer received glutamine (10 g orally three times daily) one day after the completion of paclitaxel (825 mg/m2 over 24 hours) for a duration of four days and 33 patients did not get supplement therapy. Neurologic evaluation was done by a neurologist at baseline and at least two weeks after administration of paclitaxel. In patients who received glutamine, only one patient (8%) had moderate-to severe dysesthesia in fingers or toes in comparison with 14 patients (40%) who did not received glutamine. Also, patients in glutamine group experienced less symptoms including vibration sense at the toes, interference with daily living activities, gait, and sensory deficits to pinprick compared to non-glutamine group. The results suggested that glutamine may reduce incidence and severity of peripheral neuropathy induced by paclitaxel (17).

Figure1.



3.2. Glutamate

Glutamate supplies the amino group for the biosynthesis of other amino acids, is a substrate for glutamine and glutathione synthesis, and is an important excitatory transmitter in the brain. Glutamate taken up by astroglial cells can be metabolized and converted to glutamine. Glutamate also can be ingested by dietary protein or with foods containing glutamate like soy, fish and oyster (32).

Randomized, placebo-controlled, double-blinded pilot study by Loven et al., investigated the protective effect of glutamate supplementation on paclitaxel-induced peripheral neuropathy. On the first day of chemotherapy, 43 participants (age range: 35–80 years) with advanced epithelial ovarian cancer or primary peritoneal carcinomatosis received glutamate 500 mg three times daily half an hour before or two hours after a meal, and 20 patients got placebo. This supplementation intervention was continued throughout the period of six cycles of chemotherapy until three weeks after the end of chemotherapy. Patients received at least six cycles of 175 mg/m2 paclitaxel given over a three hours infusion and carboplatin over a 30 minutes infusion on same day every three or four weeks. Complete neurological examination is done by using a Dantec Keypoint or Nicolet Voyager electromyograph (EMG) and self-evaluation questionnaire (pain, numbness, tingling and muscle weakness) and clinical evaluations at beginning of chemotherapy, before each cycle and three weeks after completion of the sixth cycle. Electrodiagnostic evidence showed 30.4% of glutamate group and 30% of placebo group developed neuropathy, indicative of no significant difference between two groups. Also Results showed that there was no significant difference in the frequency of signs and symptoms between the two groups. However there was a significance difference regard to pain sensation and patients who received glutamate supplements experienced less pain sensation (P = 0.011) (18).

Acetyl-L-carnitine

L-carnitine is an amino acid that is made in the human brain, liver, and kidneys. It helps the body turn fat into energy and used for weight loss and may have an impact on brain function, heart, muscle contraction and peripheral nervous system. L-carnitine converts to acetyl-L-carnitine and propionyl-L-carnitine in the body, but the benefits of these compounds have not been identified clearly. Generally, L-carnitine uses for L-carnitine deficiency and disorders of heart and blood vessels, and serious kidney disease (33).

Flatters et al., investigated the efficacy of acetyl-l-carnitine (ALC) to prevent and treat paclitaxel-induced pain in an animal study. Twenty rats received either 50 or 100 mg/kg ALC and 10 rats received distilled water orally for 21 days in the prophylactic model. Paclitaxel administration occurred on days 7, 12, 16, 21, 23, 25, 27, 30, 33, and 36. Results of von-frey test showed that ALC prevented the development of mechanical hypersensitivity. In the treatment model when paclitaxel-induced pain is clearly visible, 13 rats received 100 mg/kg ALC and 14 rats received distilled water for 10 days. Treatment model also showed decrease of pain in ALC group. This study shows that ALC may be useful in the prevention and treatment of chemotherapy-induced painful peripheral neuropathy (28).

Randomized, controlled study by Badary et al., was investigated ALC effects on incidence and severity of paclitaxel induced peripheral neuropathy. Patients with breast cancer (age range: 20-65 years) received paclitaxel at 135 mg/m2 every week. Twenty patients received ALC (1000 mg three times daily) during three paclitaxel courses. In other group, 20 patients received placebo during three paclitaxel courses. For follow-up, incidence and severity of sensory and motor TIPN was evaluated. Also, patients received weekly follow-up card and for self-evaluation and reporting of the frequency and the severity of sensory and motor TIPN. Also, serum nerve growth factor (NGF) was estimated at baseline and end of the study. In first course of chemotherapy, 11 patients in ALC group and 16 patients in placebo group developed sensory neuropathy (second course: 10 in ALC group vs. 17 in placebo group, third course: 6 in ALC group vs. 18 in placebo group). Six patients in ALC group vs. 11 in placebo group developed motor neuropathy (second course: 3 in ALC group vs. 12 in placebo group, third course: 3 in ALC group vs. 17 in placebo group). At baseline, NGF levels in ALC group were lower than placebo group (1.9 vs. 9.5 respectively). At the end of study NGF level in ALC group increased despite of decrease in placebo group (5.4 vs. 2.4 respectively). Delta NGF level change was significantly different between two arms. Results showed that in the first course of chemotherapy there was no significant difference in incidence of sensory and motor neuropathy but in second and third course there was a significant difference in both sensory and motor neuropathy incidence (26).

Hershman et al., randomized, double-blind trial also compared ALC (1000 mg three times daily) with placebo in 409 women (median age: 52-53 years) undergoing adjuvant taxane-based chemotherapy for breast cancer. Patients received one of the following regimens: paclitaxel at 80 mg/m2 for 12 cycles every week; paclitaxel at 175 mg/m2 for four cycles every two weeks; paclitaxel at 175 mg/m2 for six cycles every two weeks; docetaxel at 75 mg/m2 for four cycles every three weeks; or docetaxel at 75 mg/m2 for six cycles every three weeks. FACT-NTX scale (11-item neurotoxicity component of the Functional Assessment of Cancer Therapy-Neurotoxicity/Taxane) was measured at the weeks 12, 24, 36, 52, and 104. For both treatment groups, 104-week NTX scores were statistically significantly different compared to baseline and NTX scores were reduced from baseline in both groups. NTX scores for acetyl-L-carnitine group was lower than placebo in all follow-up weeks that showed TIPN worsening. This large RCT shows that despite evidence from preclinical and phase II studies, ALC is not effective in prevention of TIPN (19).

Omega-3

Omega-3 fatty acids such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are found in fatty fish, fish oil, flaxseed, and canola oil. The omega-3 fatty acids are antithrombotic and anti-inflammatory and shown beneficial cardioprotective and anti-arrhythmic effects (34).

In a randomized controlled trial study, the efficacy of omega-3 in reducing the incidence and severity of paclitaxel-induced peripheral neuropathy was investigated. Patients with breast cancer (age range: 30-70 years) were randomized to receive either the omega-3 fatty acid pearls, 640 mg three times a day or placebo during chemotherapy with paclitaxel and one month after the end of the treatment. Patients received four cycles of paclitaxel at 175 mg/m2 on over 3 hours infusion every three weeks. Incidence of neuropathy and severity was measured one month after chemotherapy by reduced total neuropathy score (rTNS) and nerve conduction study. Twenty-one patients from 30 patients taking omega-3 fatty acid supplement did not develop neuropathy and 11 patients from 27 patients in the placebo group did not developed neuropathy. In omega-3 group, four patients developed mild neuropathy (score 1-10), five patients developed moderate neuropathy (score 10-20) and severe neuropathy (score 20-28) did not develop in any patient. In placebo group, 10 patients developed mild neuropathy, five patients developed moderate neuropathy and one patient developed severe neuropathy. Incidence of peripheral neuropathy was significantly lower in the omega-3 group but paclitaxel-induced peripheral neuropathy severity did not show significant difference between two arms of the study. So, the study revealed that omega-3 fatty acids can be a good neuroprotective agent for prophylaxis against paclitaxel-induced peripheral neuropathy (20).

In a clinical trial by Anoushirvani et al., the effects of omega-3 on the incidence and severity of peripheral neuropathy in patients receiving taxol-based chemotherapy were evaluated. Twenty-one patients with a solid tumor (age range: 30-70 years) received 640 mg omega-3 three times a day and 21 patients with same inclusion criteria received placebo after the onset of chemotherapy and up to three months after its suspension. Electrophysiological evaluation was measured by a neurologist before the onset of chemotherapy and at months one and three. 28.6% of patients who received omega-3 supplement developed peripheral neuropathy in comparison with 71.4% of patients in the placebo group. In omega-3 group, four patients developed mild neuropathy and one patient developed medium and one with severe neuropathy. Placebo group consisted of seven patients with mild neuropathy, four with medium neuropathy and four with sever neuropathy. There was a significant difference between omega-3 groups and the placebo group regard to the incidence of TIPN but the severity of TIPN between two groups was not significantly different. This study shows that omega-3 may be effective to reduce the incidence of paclitaxel-induced peripheral neuropathy (21).

Vitamin E

Vitamin E or tocopherol is a fat-soluble compound. It is an important vitamin that is essential for proper function of organs in body and found in a variety of foods including almonds, vegetable oils, and cereals (35).

A phase II trial of vitamin E supplementation on prevention of paclitaxel-induced peripheral neuropathy in patients with solid or non-myeloid malignancy showed beneficial effects. The intervention group consisted of 16 patients (median age: 56.8) receiving chemotherapy with synthetic DL-alfa-tocopheryl acetate supplementation (300 mg twice daily) during chemotherapy and up to three months after chemotherapy. Control group consisted of 16 patients (median age: 57.2) treated with chemotherapy without vitamin E. Patients received paclitaxel at 175 mg/m2 plus carboplatin (or epirubicin) every three weeks for six cycles. Electrophysiological and clinical evaluation was measured by a neurologist. NSS (Neurological Symptom Score) and NDS (Neurological Disability Score) was used for clinical evaluation. Neurological tests assessed at baseline, after third and sixth courses of chemotherapy and three months after its suspension. In vitamin E group, one patient developed minor neuropathy (placebo group=3), two patients with moderate neuropathy (placebo group=4) and no one developed a severe neuropathy (placebo group=3). Peripheral neuropathy was occurred in 18.7% of patients in vitamin E supplementation group and in 62.5% of patients in control group. The incidence of peripheral neuropathy was significantly different however the severity of neuropathy was not significantly different between two groups (22).

In another study by Shamsaei et al., preventive effect of vitamin E on patients with taxol-induced neuropathy was investigated. Patients (age >18 years) with breast cancer were randomized into two groups. Treatment group consisted of 35 patients who received vitamin E (400 units twice daily) and 35 patients took placebo in the control group. Clinical and electrophysiological assessment conducted by a neurologist. Results indicated that vitamin E can reduce amplitude of sural nerve action potential. However, there was no statistically significant differentiation on preventing the peroneal and tibial nerve involvement between two groups in the study. These findings suggested that vitamin E is less effective on motor neuron involvement but can decrease the risk of sensory nerve damage (23).

Anoushirvani et al., investigated effects of vitamin E on the incidence of TIPN. In this clinical trial, 21 patients with a solid tumor (age range: 30-70 years) received vitamin E (300 mg two times a day) and 21 patients with same inclusion criteria received placebo after the onset of chemotherapy until three months later. Before onset of chemotherapy and at first and third months, patients undergo an electrophysiological and clinical evaluation by a neurologist. 33.3% patients who received vitamin E and 71.4% of control group develop TIPN. Vitamin E group consisted of three patients with mild neuropathy,

three patients with moderate neuropathy and one patient with severe neuropathy. Placebo group consisted of seven patients with mild neuropathy, four with moderate neuropathy and four with severe neuropathy. There was statistically significant difference between two groups regarding to the incidence of TIPN however severity was not significantly different (22).

A phase II, open-label randomized controlled study was conducted in patients receiving taxane-based chemotherapy to estimate effects of vitamin E supplement on preventing TIPN. 140 patients (age > 18 years) with solid or non-myeloid malignancy were randomly divided equally to a group using vitamin E at a dose of 400 mg twice daily and a group without feeding vitamin E at start of chemotherapy and for one month after its completion. Patients received paclitaxel (with or without carboplatin) median cumulative dose over 683 mg/m2 or docetaxel (with or without cyclophosphamide) median cumulative dose at 225 mg/m2. National Cancer Institute-Common Toxicity Criteria for adverse events (CTCAE v. 5.0) and Clinician-judged peripheral neuropathy assessment used for evaluation purposes. Fifty-two patients of each group developed grade 2 or higher neuropathy. Time to onset neuropathy was eight weeks for vitamin E group vs. five weeks for control group and duration of neuropathy was five weeks for vitamin E group vs. 12.5 weeks for control group. Results showed that vitamin E is effective on reducing duration of neuropathy while fails to decrease the incidence and time to onset of neuropathy (24).

B vitamins

Vitamin B comprises a class of water-soluble complexes. They have very important molecular functions in human body. There are eight major types of vitamin B denoted as vitamin B1 (thiamine), B2 (riboflavin), B3 (niacin), B5 (pantothenic acid), B6 (pyridoxine), B7 (biotin), B9 (folate), and B12 (cobalamin). Each of these vitamin B types perform different functions in the human body (36).

A randomized, placebo-controlled trial by Schloss et al,. investigated efficacy of vitamin B complex in prevention of CIPN. The study included 71 participants (age >18 years) on chemotherapy regimen that included oxaliplatin, taxanes or vincristine. Participants were divided to a B group vitamin (one capsule of 50 mg of thiamine, 20 mg of riboflavin, 100 mg of niacin, 163.5 mg of pantothenic acid, 30 mg of pyridoxine, 500 µg of folate, 500 µg of cyanocobalamin, 500 µg of biotin, 100 mg of choline and 500 µg of inositol daily) or placebo taken with or after meals. Primary outcome was a change in the TNS including pre-chemotherapy commencement, after chemotherapy (two to four weeks) and 12 weeks post-chemotherapy completion. Secondary outcomes included serum vitamin B levels, quality of life, pain inventory and the patient neurotoxicity questionnaires that recorded at baseline, 12, 24 and 36th weeks. Results showed no statistical significance for B group vitamin compared with placebo in prevention of CIPN ($p = 0.73$) (25).

The animal study by Hamity et al., evaluated vitamin B3 effect on paclitaxel-induced peripheral neuropathy. Nicotinamide riboside (third form of vitamin B3) at a dose of 200 mg/kg daily began seven days before paclitaxel administration and continued for 24 days. Nicotinamide riboside prevented the development of tactile hypersensitivity and blunted place escape–avoidance behaviors, while did not interfere with the myelosuppressive effects of paclitaxel (29).

A case study by Schloss et al., showed a hopeful result for B12 administration on decrease of TIPN. Neurological conduction studies and Total neuropathy score (TNS) was used for evaluation. After administration of docetaxel (75 mg/m2) and cyclophosphamide (600 mg/m2) every three weeks for four cycles, the patient's neurological test shows TIPN grades 2 to 3 on NCI-CTC scales (National Cancer Institute- Common Toxicity Criteria). Patient received vitamin B12 (1000 µg intramuscularly and 1000 µg orally daily) and B complex vitamins continued for two months. The patient TIPN reversed to grade 1 on NCI-CTC scales (27).

Discussion

To the best of our knowledge, this is the first review look into prevention and management of TIPN with natural products exclusively. Many patients who receive taxane-based chemotherapy develop a disabling and painful neuropathy. In most times, CIPN is limited to treatment course but sometimes, it can be long term and continued after. Understanding mechanism of taxene-induced neuropathy is necessary to find an effective intervention. TIPN is a length-dependent axonal sensory injury that is related to dosage, infusion time, comorbidity and other chemotherapy drugs that patient might receive (37). Taxanes binding to polymerized tubulins and interrupting the G2 phase of the cell cycle in cancer cells but microtubules stabilization also happens in peripheral nervous system and it causes damages to dorsal root ganglia, axons, neuronal transport of organelles, nutrients and neurotransmitters through the axons which leads to axonal degeneration and peripheral neuropathy. (38, 39). Taxanes also bind to mitochondrial β-tubulin, causing morphological and functional mitochondrial damage by increasing permeability and calcium efflux. These events trigger cancer cell apoptosis and necrosis mitochondria is damaged by taxane and decrease in level of adenosine triphosphate (ATP). Mitochondrial damages increased production of reactive oxygen species (ROS) that leads to a state of oxidative stress. Oxidative stress is occurred by taxane damages also causes ATP reduction and this increases pain sensation in patients (38, 40, 41). Another mechanism for pain induced by taxane is inflammation and transporter-mediated uptake of taxane. Most common cytokines participate in taxane-induced inflammation are IL-1β, IL-8 and TNF-α (42, 43). Furthermore, taxanes changing the activity of voltage-gated ion channels (Cav, Nav and Kv) and transient receptor potential (TRP) channels which leading to hyperexcitability of neurons and nerve injuries (44, 45).

Until now, there is no certain therapy and intervention for taxane-induced neuropathy. Acupuncture, massage, medications, and complementary therapies also can be used (46). Duloxetine is a selective serotonin and norepinephrine reuptake inhibitor (SNRI) antidepressant which consider as most common intervention but shows some complications and have high drop-out rate (47). Somnolence, dizziness, nausea, dysgeusia and constipation are most common adverse effects of duloxetine in patients with paclitaxel-induced peripheral neuropathy (48). Gabapentin and other drug interventions have adverse effects that may lead to cut off drugs. Considering all of this, we need to find a safe and effective intervention. Focus of this study was the effectiveness of complementary therapies on TIPN (Figure 1). Supplementary therapies are safe and probably do not interfere with chemotherapy drugs. Furthermore, we do not worry about drop-out the interventions. Although the data for effectiveness of supplementary therapies is limited and we need more clinical trials to use them as an option in clinical situations.

This review indicates that supplementary therapies can be effective to reduce pain and duration of TIPN and also may prevent TIPN in some degrees; although these findings need further investigations to use in clinical therapies. Glutamine seems to be effective (17) but its single article is not reliable because lack of control group and small sample size and we need further investigations. Glutamine mechanism in peripheral neuropathy is unknown but there are some proposed mechanisms. The severity of chemotherapy induced neuropathy is related to reduction of serum levels of nerve growth factor (NGF) and glutamine demonstrated that can increase NGF mRNA in animal models (49, 50). Another suggested mechanism is that glutamine can enhance the microtube stability (51). Glutamine is a precursor amino acid for excitatory neurotransmitters like glutamate. In most tissues, glutamine is converted to glutamate by glutaminase and glutamate converted to glutamine by glutamine-synthetase (52-54). Glutamine and glutamate may change the understanding of pain in cerebral cortex and it can be possible mechanism for comfort pain (52). Long-term glutamate supplementation can reduce pain sensation but it seems ineffective on other aspects of TIPN. Conclusion of this article do not suggest glutamate as an effective supplement for TIPN (18). Glutamine and glutamate are closely related amino acids and they can turn to each other (55), so results between glutamine study (17) and glutamate study (18) is conflicting. The method for each article is different. Glutamine study evaluated short-term period after high dose of paclitaxel but in glutamate study, lasted for six months. Also, glutamine study had no placebo group and the neurological assessments was limited and insufficient.

We found one animal study (28) and two RCT about ALC (19, 26). ALC showed hopeful results in animal studies and first clinical study but in large sample size and long-term clinical stages failed to protect neuropathy development and even may worsen the neuropathy. The evaluation method used for study by Badary et al., was quantitative and self-evaluation which can be confusing. ALC shows central anti-nociceptive and neuroprotective results in patients with diabetic neuropathy. These actions may be related to TIPN improvement mechanisms of ALC (56, 57). Two RCTs suggested omega-3 supplementation as an effective intervention in three months follow up duration but we need long-term RCTs to take a solid conclusion. Also, EPA and DHA concentration between omega-3 group and placebo group was evaluated and was significantly decreased in placebo group (20). Omega-3 have an anti-inflammatory effect that may be related to decreasing neuropathic symptoms. Omega-3 regulate the cytokines, chemokines and growth factor which released by cells to confront with tumor cells (58). Another possible mechanism for Omega-3 reduction of pain sensation is related to overexpression of the free fatty acid receptor 1 (FFA1) receptor in the spinal cord. FFA1 receptor activation increase β-endorphin, noradrenaline, and serotonin release which can decrease neuropathy symptoms (59-61). We investigate two randomized controlled trials (21, 23) and two clinical trials without placebo group (22, 24) for vitamin E and all of them suggested that vitamin E can be useful in some levels. Vitamin E is shown hopeful effects on incidence and duration of neuropathy. However, in the last RCT by Heiba et al., on 140 patients for three months, reduction of neuropathy duration was the only effective result of vitamin E. This study is largest study for effect of vitamin E on TIPN and despite other articles which used electrophysiological and clinical evaluations, this study used CTCAE v. 5.0 for evaluation that is closer to actual clinical situation. One big limitation for this study was absence of placebo group. Safety of vitamin E evaluated by recording all adverse effect in patients and comparing them between two groups. Vitamin E did not show any possible adverse effect and well tolerated (22). There is no investigations for mechanism of vitamin E on chemotherapy related neuropathy, however it is demonstrated that vitamin E improve diabetic neuropathy in rat through antioxidant effects and by regulating inflammatory cytokines (62). Vitamin E acting as a free radical scavenger which can be helpful in preventing diseases that are associated with oxidative stress such as TIPN (22).

One RCT for vitamin B-complex supplements suggested that it cannot protect from neuropathy (25). Vitamin B3 in an animal study (29) showed hopeful results but there is no RCTs that focus on effectiveness of vitamin B3 on TIPN. Nicotinamide riboside is NAD+ (nicotinamide adenine dinucleotide) precursor and there is a concern that NAD+ may be related to tumorigenesis. Although nicotinamide riboside did not interfere with myelosuppressive effects of paclitaxel. Lower level of vitamin B12 may related to TIPN. Some patients with developed neuropathy in placebo group shows lower blood level of vitamin B12 than baseline (25). Blood level of vitamin B12 was lower than baseline after chemotherapy but other B vitamins blood level did not reduce (27). A case study also demonstrated that vitamin B12 can be effective

against TIPN. Mechanism of action for B group vitamins is not clear although there is a possible mechanism for B12 vitamin. Vitamin B12 have an important role in myelination and neuron repairmen that can improve neuropathy (63).

In a randomized study by Mondal et al., the efficacy of vitamin E, ALC, glutamine, and methylcobalamine were compared. Patients categorized in four groups: vitamin E: 400 mg once daily; ALC: 250 mg once daily; glutamine: 10 mg three times daily and methylcobalamine: 500 µg daily. All drugs were started at the onset of symptoms after paclitaxel administration. CTCAE v 4.02 (Common Terminology Criteria for Adverse Events) was used for assessments. Changes in scores for sensory, motor and pain symptoms over the study period were compared. All four drugs were effective in the alleviation of all peripheral neuropathy symptoms (pain, motor and sensory symptoms) while vitamin E and methylcobalamine were both more effective than glutamine and ALC (64). Exact cause of beneficial effects in this study cannot be specified due to absence of placebo group.

There are some limitations that avoid us to reach a solid result. Most of the articles investigated the effects of complementary therapies on CIPN as general and number of articles that investigate on taxane-based chemotherapy regimen is limited. We try to choose articles with focus on just taxane-based chemotherapy. In articles that included to our study, differences in neuropathy evaluation scales are a major problem and is probably the main reason for conflicting results. Duration of follow up is also different. Most of research did not evaluate long-term results, except glutamate (18) and ALC (19). Also, there are small sample sizes and patient selection criteria is not the same in the articles. On the other hands, purposes of the studies maybe different among some of them. Some investigate interventions for neuropathy prevention while others investigate interventions for improvements of neuropathy.

The result of this article showed that supplements can be used as an auxiliary intervention in reducing TIPN symptoms along with other pharmacological and non-pharmacological interventions. However, before use them as a clinical option, we need more investigations. If this effectiveness confirms in further studies, they can be used as a routine treatment to reduce the severity and incidence of TIPN and then prevent dose modification of taxanes, avoiding delay in treatment process.

Conclusion

In this study we have investigated 10 clinical trials, one case study and two animal studies. Total sample size of patients that were participated in the RCTs were 1033. In conclusion, vitamin E, omega 3, glutamine, B3 and B12 vitamin can be effective on preventing and improvement of TIPN. Paclitaxel at 175 mg/m2 every 3-4 weeks was the most chemotherapy regimen used in the method of researches. Also, breast cancer was the most common type of cancer that used. The duration range of the studies was during chemotherapy cycles and for at least two weeks and at most two years after chemotherapy. Among supplements studied on TIPN, vitamin E was the most common researched supplement which four RCTs have investigated its effectiveness on TIPN. Despite effectiveness on animal studies, ALC shows that worsen TIPN outcome. Glutamate cannot prevent TIPN in long-term although may be effective on pain sensation. However, we need still large sample size RCTs and further research to get a solid conclusion to use supplemental preparations as an actual clinical intervention.

Conflict of Interests

There is no conflict of interests.

References

1. Gewandter JS, Kleckner AS, Marshall JH, et al. Chemotherapy-induced peripheral neuropathy (CIPN) and its treatment: an NIH Collaboratory study of claims data. Support Care Cancer. 2020;28(6):2553-62.
2. Salehifar E, Janbabaei G, Hendouei N, Alipour A, Tabrizi N, Avan R. Comparison of the efficacy and safety of pregabalin and duloxetine in taxane-induced sensory neuropathy: a randomized controlled trial. Clin Drug Investig. 2020;40(3):249-57.
3. Song SJ, Min J, Suh SY, et al. Incidence of taxane-induced peripheral neuropathy receiving treatment and prescription patterns in patients with breast cancer. Support Care Cancer. 2017;25(7):2241-8.
4. Timmins HC, Li T, Kiernan MC, et al. Taxane-induced peripheral neuropathy: differences in patient report and objective assessment. Support Care Cancer. 2020;28(9):4459-66.
5. Pivot X, Koralewski P, Hidalgo J, et al. A multicenter phase II study of XRP6258 administered as a 1-h iv infusion every 3 weeks in taxane-resistant metastatic breast cancer patients. Ann Oncol. 2008;19(9):1547-52.
6. De Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet. 2010;376(9747):1147-54.
7. Velasco R, Bruna J. Taxane-induced peripheral neurotoxicity. Toxics. 2015;3(2):152-69.
8. Grisold W, Cavaletti G, Windebank AJ. Peripheral neuropathies from chemotherapeutics and targeted agents: diagnosis, treatment, and prevention. Neuro-oncol. 2012;14(suppl_4):iv45-iv54.
9. Horwitz S. Taxol (paclitaxel): mechanisms of action. Ann Oncol. 1994;5:S3-6.

10. Pace A, Bove L, Aloe A, et al. Paclitaxel neurotoxicity: clinical and neurophysiological study of 23 patients. Ital J Neurol Sci. 1997;18(2):73-9.

11. Argyriou AA, Bruna J, Marmiroli P, Cavaletti G. Chemotherapy-induced peripheral neurotoxicity (CIPN): an update. Crit Rev Oncol Hematol. 2012;82(1):51-77.

12. De Iuliis F, Taglieri L, Salerno G, Lanza R, Scarpa S. Taxane induced neuropathy in patients affected by breast cancer: literature review. Crit Rev Oncol Hematol. 2015;96(1):34-45.

13. Loprinzi CL, Reeves BN, Dakhil SR, Sloan JA, Wolf SL, Burger KN, et al. Natural history of paclitaxel-associated acute pain syndrome: prospective cohort study NCCTG N08C1. J Clin Oncol. 2011;29(11):1472.

14. Tanabe Y, Hashimoto K, Shimizu C, et al. Paclitaxel-induced peripheral neuropathy in patients receiving adjuvant chemotherapy for breast cancer. Int J Clin Oncol. 2013;18(1):132-8.

15. Flatters SJ, Dougherty PM, Colvin LA. Clinical and preclinical perspectives on chemotherapy-induced peripheral neuropathy (CIPN): a narrative review. Brit J Anaesthesia. 2017;119(4):737-49.

16. Raja SN, Haythornthwaite J, Pappagallo M, et al. Opioids versus antidepressants in postherpetic neuralgia: a randomized, placebo-controlled trial. Neurology. 2002;59(7):1015-21.

17. Vahdat L, Papadopoulos K, Lange D, et al. Reduction of paclitaxel-induced peripheral neuropathy with glutamine. Clin Cancer Res. 2001;7(5):1192-7.

18. Loven D, Levavi H, Sabach G, et al. Long-term glutamate supplementation failed to protect against peripheral neurotoxicity of paclitaxel. Eur J Cancer Care. 2009;18(1):78-83.

19. Hershman DL, Unger JM, Crew KD, et al. Two-year trends of taxane-induced neuropathy in women enrolled in a randomized trial of acetyl-L-carnitine (SWOG S0715). J Natl Cancer Inst. 2018;110(6):669-76.

20. 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(1):1-8.

21. 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(10):1857.

22. 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(3):237-44.

23. Shamsaei G, Ahmadzadeh A, Mehraban N. The vitamin E preventive effect on Taxol-induced neuropathy among patients with breast cancer: A randomized clinical trial. Jundishapur Journal of Natural Pharmaceutical Products. 2017;12(4); e65027.

24. Heiba MA, Ismail SS, Sabry M, Bayoumy WAE, Kamal KAA. The use of vitamin E in preventing taxane-induced peripheral neuropathy. Cancer Chem Pharmacol. 2021;88(6):931-9.

25. Schloss JM, Colosimo M, Airey C, Masci P, Linnane AW, Vitetta L. A randomised, placebo-controlled trial assessing the efficacy of an oral B group vitamin in preventing the development of chemotherapy-induced peripheral neuropathy (CIPN). Support Care Cancer. 2017;25(1):195-204.

26. Badary O. Effect of acetyl-l-carnitine on the incidence and the severity of paclitaxel-induced peripheral neuropathy in cancer patients. Al-Azhar Journal of Pharmaceutical Sciences. 2014;50(2):14-30.

27. Schloss JM, Colosimo M, Airey C, Vitetta L. Chemotherapy-induced peripheral neuropathy (CIPN) and vitamin B12 deficiency. Support Care Cancer. 2015;23(7):1843-50.

28. Flatters SJ, Xiao W-H, Bennett GJ. Acetyl-L-carnitine prevents and reduces paclitaxel-induced painful peripheral neuropathy. Neurosci Lett. 2006;397(3):219-23.

29. Hamity MV, White SR, Walder RY, Schmidt MS, Brenner C, Hammond DL. Nicotinamide riboside, a form of vitamin B3 and NAD+ precursor, relieves the nociceptive and aversive dimensions of paclitaxel-induced peripheral neuropathy in female rats. Pain. 2017;158(5):962-72.

30. Smith RJ, Wilmore DW. Glutamine nutrition and requirements. JPEN J Parenter Enteral Nutr. 1990;14:94S-9S.

31. Klimberg VS, McClellan JL. Glutamine, cancer, and its therapy. Am J Surg. 1996;172(5):418-24.

32. Zhou Y, Danbolt NC. Glutamate as a neurotransmitter in the healthy brain. J Neural Transm (Vienna). 2014;121(8):799-817.

33. Evans AM, Fornasini G. Pharmacokinetics of L-carnitine. Clin Pharmacokinetics. 2003;42(11):941-67.

34. Kris-Etherton PM, Taylor DS, Yu-Poth S, et al. Polyunsaturated fatty acids in the food chain in the United States. Am J Clin Nutr. 2000;71(1):179S-88S.

35. L Abner E, A Schmitt F, S Mendiondo M, L Marcum J, J Kryscio R. Vitamin E and all-cause mortality: a meta-analysis. Curr Aging Sci. 2011;4(2):158-70.

36. Tylewicz U, Inchingolo R, Rodriguez-Estrada M. Nutraceutical and Functional Food Components. Elsevier Amsterdam, The Netherlands:; 2017.

37. Carlson K, Ocean AJ. Peripheral neuropathy with microtubule-targeting agents: occurrence and management approach. Clin Breast Cancer. 2011;11(2):73-81.

38. Klein I, Lehmann HC. Pathomechanisms of paclitaxel-induced peripheral neuropathy. Toxics. 2021;9(10):229.

39. Fukuda Y, Li Y, Segal RA. A mechanistic understanding of axon degeneration in chemotherapy-induced peripheral neuropathy. Front Neurosci. 2017;11:481.

40. Shim HS, Bae C, Wang J, et al. Peripheral and central oxidative stress in chemotherapy-induced neuropathic pain. Mol Pain. 2019;15:1744806919840098.

41. Weaver BA. How Taxol/paclitaxel kills cancer cells. Mol Bol Cell. 2014;25(18):2677-81.

42. Al-Mazidi S, Alotaibi M, Nedjadi T, Chaudhary A, Alzoghaibi M, Djouhri L. Blocking of cytokines signalling attenuates evoked and spontaneous neuropathic pain behaviours in the paclitaxel rat model of chemotherapy-induced neuropathy. Eur J Pain. 2018;22(4):810-21.

43. Szklener K, Szklener S, Michalski A, et al. Dietary Supplements in Chemotherapy-Induced Peripheral Neuropathy: A New Hope? Nutrients. 2022;14(3):625.

44. Bae EH, Greenwald MK, Schwartz AG. Chemotherapy-induced peripheral neuropathy: mechanisms and therapeutic avenues. Neurotherapeutics. 2021;18(4):2384-96.

45. Sałat K. Chemotherapy-induced peripheral neuropathy: part 1—current state of knowledge and perspectives for pharmacotherapy. Pharmacol Rep. 2020;72(3):486-507.

46. 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.

47. Smith EML, 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(13):1359-67.

48. Otake A, Yoshino K, Ueda Y, et al. Usefulness of duloxetine for Paclitaxel-induced peripheral neuropathy treatment in gynecological cancer patients. Anticancer Res. 2015;35(1):359-63.

49. De Santis S, Pace A, Bove L, et al. Patients treated with antitumor drugs displaying neurological deficits are characterized by a low circulating level of nerve growth factor. Clin Cancer Res. 2000;6(1):90-5.

50. Gwag B, Sessler F, Robine V, Springer J. Endogenous glutamate levels regulate nerve growth factor mRNA expression in the rat dentate gyrus. Mol cells. 1997;7(3):425-30.

51. Boyle FM, Wheeler HR, Shenfield GM. Glutamate ameliorates experimental vincristine neuropathy. J Pharmacol Exp Ther. 1996;279(1):410-5.

52. Kandel ER, Schwartz JH, Jessell TM, Siegelbaum S, Hudspeth AJ, Mack S. Principles of neural science: McGraw-hill New York; 2000.

53. Daikhin Y, Yudkoff M. Compartmentation of brain glutamate metabolism in neurons and glia. J Nutr. 2000;130(4):1026S-31S.

54. Savarese DM, Savy G, Vahdat L, Wischmeyer PE, Corey B. Prevention of chemotherapy and radiation toxicity with glutamine. Cancer Treat Rev. 2003;29(6):501-13.

55. Tapiero H, Mathe G, Couvreur P, Tew K. II. Glutamine and glutamate. Biomed Pharmacother. 2002;56(9):446-57.

56. Di Stefano G, Di Lionardo A, Galosi E, Truini A, Cruccu G. Acetyl-L-carnitine in painful peripheral neuropathy: a systematic review. J Pain Res. 2019;12:1341.

57. Lowitt S, Malone J, Salem A, Korthals J, Benford S. Acetyl-L-carnitine corrects the altered peripheral nerve function of experimental diabetes. Metabolism. 1995;44(5):677-80.

58. Elinav E, Nowarski R, Thaiss CA, Hu B, Jin C, Flavell RA. Inflammation-induced cancer: crosstalk between tumours, immune cells and microorganisms. Nature Rev Cancer. 2013;13(11):759-71.

59. Freitas RD, Costa KM, Nicoletti NF, Kist LW, Bogo MR, Campos MM. Omega-3 fatty acids are able to modulate the painful symptoms associated to cyclophosphamide-induced-hemorrhagic cystitis in mice. J Nutr Biochem. 2016;27:219-32.

60. Nakamoto K, Nishinaka T, Sato N, Aizawa F, Yamashita T, Mankura M, et al. The activation of supraspinal GPR 40/FFA 1 receptor signalling regulates the descending pain control system. Brit J Pharmacol. 2015;172(5):1250-62.

61. Freitas RD, Campos MM. Protective effects of omega-3 fatty acids in cancer-related complications. Nutrients. 2019;11(5):945.

62. Kuhad A, Chopra K. Tocotrienol attenuates oxidative–nitrosative stress and inflammatory cascade in experimental model of diabetic neuropathy. Neuropharmacol. 2009;57(4):456-62.

63. Wu F, Xu K, Liu L, et al. Vitamin B12 enhances nerve repair and improves functional recovery after traumatic brain injury by inhibiting ER stress-induced neuron injury. Front Pharmacol. 2019:406.

64. Mondal S, Choudhury KB, Sharma S, Gupta A, Dutta S. Comparative study among glutamine, acetyl-L-carnitine, vitamin-E and methylcobalamine for treatment of paclitaxel-induced peripheral neuropathy. Clin Cancer Investig J. 2014;3(3):213.

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