



A review of complementary therapies with medicinal plants for chemotherapy-induced peripheral neuropathy

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ABSTRACT

Introduction: Chemotherapy-induced peripheral neuropathy (CIPN) is a progressive, prolonged, and often irreversible side effect of many chemotherapeutic agents. The development of neuropathic pain is still poorly managed by clinically available drugs at present.

Methods: In this mini-review, we summarized the current knowledge of pathobiology for CIPN, and selected evidence on the application of complementary therapies in experimental studies.

Results: Medicinal plants are considered to be the most common complementary therapy modalities for CIPN. Therefore, we identified ten medicinal herbal extracts as well as their phytochemicals, and three herbal formulas. Multiple complementary therapies have been used and studied for decades, and their effects against CIPN are focus on anti-oxidative activity. However, there is still controversial due to the diverse manifestations of different antineoplastic agents and complex drug interactions.

Conclusions: Novel therapies or drugs that have proven to be effective in animals require further investigation, so confirmation of their efficacy and safety will require time.

1. Introduction

Cancer is the second most common cause of death worldwide, behind only cardiovascular disease. The treatment of cancer has progressed rapidly in the past decades, and survival rates are improving.^{1,2} Chemotherapy plays an indispensable role in the current cancer treatment guidelines to prolong survival. However, it is widely recognized that the use of chemotherapy results in side effects such as hair loss, vomiting, leukopenia, or neuralgia, which adversely affect patients' quality of life. A report by the Oncology Nursing Society found that chemotherapy-induced peripheral neuropathy (CIPN) has been an important issue in cancer care since 2009.³ CIPN is a dose-limiting neurotoxicity of chemotherapeutic drugs that afflicts between 30% and 40% of patients undergoing treatment.⁴ It has been pathologically described as functional impairment of neurons characterized by a delay

event of oxidative stress, inflammation, apoptosis, and electrophysiological disturbances.⁵

CIPN is a major oncological problem caused by the treatment of a malignant disease with chemotherapeutic agents. It affects the peripheral sensory and/or motor systems and causes numbness, pain, burning, tingling, heat and cold hyperalgesia, and mechanical allodynia, as well as reduced motor function.⁵ After completing treatment with chemotherapy, approximately 68% of patients in the first month and 30% of patients over 6 months still have CIPN.⁶ Moreover, after completion of treatment, CIPN may continue to develop and worsen, in a phenomenon known as "coasting".⁷ CIPN and its associated complications lead to a dose reduction of chemotherapy, thereby limiting therapeutic efficacy. CIPN adds a substantial burden on the medical care required for patients, increases healthcare costs, and affects patients' quality of life.⁷ Current treatment options for CIPN are suboptimal and

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controversial. It is necessary to develop more effective treatment strategies for chemotherapy-induced peripheral neuropathy. Emerging evidence suggests that complementary- and alternative medicine-(CAM-) based therapeutic modalities have the potential to modulate the immune system, alleviate the inflammatory cascade, and restore nerve damage while improving the patient's quality of life. In this context, we review the complementary medicine-based therapies for treatment of CIPN. However, before going into these items, it is necessary to understand the architecture of the peripheral nervous system (PNS) and current understanding of the molecular mechanisms of the pathology of CIPN.

2. Structural architecture of peripheral nerves

The PNS is composed of neuronal cells, glial cells, and stromal cells, which convey neural signals between the central nerve system (CNS) and the rest of the body. Efferent divisions (motor and autonomic) receive signals through their dendrites from CNS neurons, primarily using the neurotransmitter acetylcholine, among others. The afferent (sensory) division receives signals through specialized receptors, such as Meissner's corpuscles for fine sensation, and others.⁸ Unlike the CNS, the PNS has an intrinsic ability for repair and regeneration. Injury to the PNS immediately elicits the migration of phagocytes and Schwann cells to the lesion site to clear away debris such as damaged tissue.⁸ After that, Schwann cells release neurotrophic factors that govern the steps of neuro-regeneration. Human axon growth rates can reach 1–2 mm/day in distal segments and 2–3 mm/day in proximal segments. However, the degree of peripheral neuropathy still depends on the reversibility and range after nerve damage. Several etiologies, such as genetics, chronic disease, environmental toxins, alcoholism, or the side effects of certain medications, are also important in the differentiation of actual neuropathy from other disorders.⁹ Despite the different causes, sensory abnormalities develop more often than do motor symptoms because motor neurons have greater myelination.⁸ The distal parts of the axons are the first affected, so sensory symptoms typically start symmetrically and bilaterally from the distal parts, with a proximal progression in a “stocking-glove” distribution.¹⁰

Numerous chemotherapeutic drugs are associated with neurotoxicity and PN. CIPN has been attributed to the easier penetrability of the peripheral nerves, which are accumulated and bound by chemotherapy drugs, and also to direct destruction of dorsal root ganglia (DRG) and peripheral axons.^{5,10} In contrast to the CNS, which is well-protected, the PNS lacks an efficient blood brain barrier and has less abundant lymphatic drainage, so it is more vulnerable to chemical toxins.^{11,12} Certain risk factors, including genetics, existing neuropathy, diabetes, smoking history, and decreased creatinine clearance, may aggravate the development of CIPN.⁹ Despite the many attempts to reduce such risk factors, dose reduction or discontinuation of chemotherapy is a wise approach to preventing peripheral neuropathy.⁴

3. Pathobiology of CIPN

The underlying mechanisms in different classes of chemotherapeutic agents can cause peripheral neuropathy. It is generally accepted that at the cellular level, neurotoxic chemotherapeutic agents damage microtubules and interfere with microtubule-based axonal transport, interrupt mitochondrial function, alter ionic homeostasis, or directly target DNA,¹³ subsequently leading to peripheral nerve degeneration or small fiber neuropathy. For example, taxane agents exert their antimitotic effect by disrupting the axonal microtubule structure and blocking the axonal energy supply on mitochondria in primary afferent neurons.¹⁴ Vinca alkaloids, another anti-microtubule drug, alter the neuronal cytoskeleton, thereby disrupting mitotic spindles and causing cell cycle arrest.¹⁴ Platinum agents are thought to cause CIPN by exerting damage in the DRG through mitochondrial dysfunction and neuronal apoptosis, either by DNA crosslinking or oxidative stress.¹⁵

Newer targeted drugs, such as bortezomib, eribulin, and ixabepilone, are also associated with significant incidence of peripheral neuropathy due to their effects on tubulin polymerization.^{10,15} Non-neuronal cells, also called glia, seem to be an important component of CIPN. Changes to Schwann cells in the periphery, satellite cells in the DRG, and astrocytes in the spinal cord after treatment with neurotoxic agents activate the apoptotic pathways.¹⁶ Loss of these glial cells leads to a loss of protection and nourishment of nerve fibers and impairment of action potential propagation.⁵

Besides the morphological changes caused by chemotherapy agents in CIPN, current evidence suggests involvement in the inflammatory and immune responses. The chemotherapeutic agents can cause mitochondrial DNA to adduct and defects in electron transport chain proteins, leading to mitochondrial dysfunction.^{17,18} This phenomenon is accompanied by an imbalance in the intracellular redox potential and elevation of reactive oxygen species (ROS), especially superoxides.¹⁷ These major reactive species can elicit various alterations in peripheral neurons, such as redundant mitochondrial damage leading to apoptosis, inflammation, and sequential nerve degeneration.^{17,18} These reactive species are also reported to cause damage to biomolecules such as phospholipids, which results in demyelination, oxidation of proteins, and the release of carbonyl by-products, which can sensitize transient receptor potential vanilloid (TRPV) channels, inactivate antioxidant enzymes, and destroy microtubules.¹⁷ Nuclear DNA adduction and peroxynitrite create strand breaks, activating Poly (ADP-ribose) polymerase (PARP), bax, and p53, which force the neuron towards apoptosis.¹⁹ Intracellular oxidative stress can also cause peripheral nociceptor over-excitation by elevating the levels of pro-inflammatory mediators (IL-1 β , TNF- α , bradykinin, and nerve growth factors).¹³ All these metabolic, bioenergetic, and functional deficits in neurons lead to the development and maintenance of peripheral neuropathic damage.¹⁷

Given the literature summarized above, it is clear that some kind of preventative therapy is required for CIPN in patients receiving chemotherapy. Although many hypotheses have been proposed, no definite intervention has been fully recommended for the prevention or management of CIPN.²⁰ In many cases, the chemotherapy needs to be discontinued due to incidence of CIPN, which places the lives of the patients at risk. Complementary therapies are widely used, particularly for chronic medical conditions that are difficult to resolve. Because only a limited number of treatments are available for CIPN, many patients can opt for complementary therapies such as herbal medicine, acupuncture, nutrients, sensorimotor training, or mind-body therapy such as imagery and relaxation, yoga, meditation and qigong. One of the most important complementary therapy modalities for chemotherapy-induced PN is based on medicinal plants. Therefore, the main objective of this review is to highlight and investigate the application of medicinal plants includes three herbal formulas in underlying mechanisms and to provide some insight for its future therapeutic potential.

4. Medicinal plant based complementary therapies for CIPN (Table 1)

4.1. *Acorus calamus* L

Acorus calamus (family: Araceae) has a very long history of medicinal use in the Chinese and Indian herbal traditions. It is commonly used to relieve muscle, joint, vascular, and nerve injury-associated severe inflammatory and neuropathic pain in Ayurvedic medicine. *Acorus calamus* is reported to have anti-oxidative, anti-inflammatory, neuro-protective, and calcium inhibitory effects in rat models of vincristine-induced painful neuropathy.²¹ Hydroalcoholic extract of *Acorus calamus* attenuates vincristine-induced neuropathy, including hyperalgesia and allodynia, along with decreasing the levels of superoxide anion, TNF- α , total calcium, and myeloperoxidase activity.²¹ Fiber derangement, swelling of nerve fibers, and activation of neuroglial cells (satellite cells and Schwann cells) are also attenuated significantly.²¹ Moreover,

Table 1
Summary of medicinal plants for the treatment of chemotherapy-induced peripheral neuropathy.

| Herb (plant organs) | Compound or extract | Effects |
|--|---|--|
| <i>Acorus calamus</i> L. (rhizome) | Hydroalcoholic extract ²¹ ; benzene extract ²² | Antioxidation (decrease free radicals, superoxide anion and myeloperoxidase activity; decrease damage of DNA and mitochondria) ²² ; decrease calcium level ²¹ ; anti-inflammation (decrease TNF- α) ²¹ ; neuroprotection (decrease nerve derangement and swelling; decrease activation of neuroglial cells) ²¹ |
| Cannabis species | Cannabinoid receptor agonist (AM1710, WIN55,212-2) | Analgesic effect via activating cannabinoid receptors (CB ₁ and CB ₂ receptors) ^{24, 25} |
| <i>Matricaria chamomilla</i> L. (flower) | Water extract ^{28, 29} ; apigenin ³⁰ ; quercetin ^{31–34} | Antioxidation (decrease iNOS, NO, peroxynitrite) ^{28, 32} ; anti-inflammation (decrease PGE ₂ , COX-2, NF- κ B, and TRPV1; stabilize mast cells) ^{29, 31, 33, 34} ; neuroprotection (protect dorsal horn neurons) ³² ; synergistic effects (apigenin and paclitaxel) ³⁰ |
| <i>Ginkgo biloba</i> L. (leaf) | A standardized extract (EGb 761) ^{35–39} | Antioxidation (decrease NO) ^{35, 39} ; anti-inflammation (decrease TNF- α and NF- κ B) ^{36–38} ; neuroprotection (decrease axonal degradation; increase axonal transportation) ³⁶ ; activate mu opioid receptor ³⁸ |
| <i>Salvia officinalis</i> L. (flower/leaf/stem) | Rosmarinic acid ^{40, 43} ; hydroalcoholic extract ⁴¹ ; water extract ⁴² | Antioxidation (decrease ROS; activate AMPK; decrease mitochondrial dysfunction) ^{40, 42, 43} ; anti-inflammation. ^{40, 41, 43} |
| Fritillaria species (bulbs) | Verticinone ^{45, 46} ; peimine ⁴⁷ | Antioxidation (decrease iNOS) ⁴⁶ ; anti-inflammation (decrease COX-2, TNF- α , IL-1 β and NF- κ B) ^{45, 46} ; inhibit sodium and potassium ion channel ⁴⁷ |
| <i>Curcuma longa</i> L. (rhizome) | Curcumin ^{48–53} | Antioxidation ⁴⁸ ; anti-inflammation (decrease COX-2 and BDNF) ⁵⁰ ; neuroprotection (reduce Schwann cells apoptosis and promote myelination) ^{49, 51} ; synergistic effects (combine curcumin with cisplatin, paclitaxel, or 5-fluorouracil) ^{52, 53} |
| <i>Angelica dahurica</i> Fisch.ex Hoffm. (Radix) | Ethyl acetate extract ⁵⁴ ; Auraptelen ⁵⁵ | Antioxidation (decrease iNOS and NO) ⁵⁴ ; anti-inflammation (decrease TNF- α , PGE ₂ , COX-2, and NF- κ B) ⁵⁴ ; activate serotonin 5-HT _{1A} receptors ⁵⁵ |
| <i>Camellia sinensis</i> L. (leaf) | Water extract ⁵⁶ ; epigallocatechin-3-gallate ^{57, 58} | Antioxidation (decrease nNOS/NO) ^{56, 57} ; anti-inflammation (decrease TNF- α , JNKs, and NF- κ B) ⁵⁷ ; synergistic effects ⁵⁸ |
| <i>Ocimum sanctum</i> L. (leaf/stem) | Ethyl acetate extract ^{59–62} ; apigenin ⁶³ ; rosmarinic acid ⁶⁴ ; Eugenol ⁶⁵ | Antioxidation (decrease thiobarbituric acid reactive substances and superoxide anion) ^{59–62} ; anti-inflammation (decrease COX2, PGE-2, IL-1 β , TNF- α , MMP2) ^{59, 63–65} ; decrease total calcium levels ^{60, 61} |

benzene extract of *Acorus calamus* is a source of a potent antioxidant compound, as it inhibits the generation of free radicals and protects DNA and mitochondria from oxidative damage, as revealed by in vitro assays and its efficacy in vivo²².

4.2. Cannabis species

Cannabis species have been used as medicine for thousands of years. For the cancer patient, cannabis has a number of potential benefits, especially in the management of symptoms. Cannabis is used to reduce nausea and vomiting during chemotherapy, to combat anorexia, and to treat chronic pain, insomnia, and depression.²³ The cannabinoid (CB) receptors are not activated only by phytocannabinoids from cannabis; they also react with endocannabinoids from humans, probably to assist in modulation of the response to pain.²³ Preclinical evidence suggests that cannabinoids are effective not only in the treatment but also in the prevention of chemotherapy-induced peripheral neuropathy.²³ Cannabinoids are reported to suppress the maintenance of cisplatin-, paclitaxel-, and vincristine-induced neuropathic nociception through activation of both CB₁ and CB₂ receptors or selective CB₂ receptors.^{24, 25} Prophylactic cannabinoid administration blocks the development of paclitaxel-induced neuropathic nociception during analgesic treatment and following cessation of drug delivery.²⁶ Moreover, prolonged use of CB₂ agonists for managing chemotherapy-induced neuropathy has a favorable therapeutic ratio, marked by sustained efficacy and absence of tolerance, physical withdrawal, or CB₁-mediated side effects.²⁷ Cannabinoids could be synergistic with opioids in the relief of pain. The safety profile of cannabis is acceptable, with side effects that are generally tolerable and short-lived.²⁷

4.3. Matricaria chamomilla L

Matricaria chamomilla L. (family: Asteraceae), commonly known as chamomile, is one of the most popular single-ingredient herbal teas, or tisanes. The extract of chamomile has antioxidant, antispasmodic, anxiolytic, anti-inflammatory, and some antimutagenic and cholesterol-lowering properties.²⁸ Aqueous chamomile extract has the ability to inhibit the release of PGE₂ from LPS activated RAW 264.7 macrophages

via the suppression of COX-2 gene expression and direct inhibition of COX-2 enzyme activity.²⁹ In mice, the analgesic and anti-inflammation effects of hydroalcoholic extract of *Matricaria chamomilla* are better than those of morphine on the vincristine- and cisplatin-induced peripheral neuropathy model.³⁰ Apigenin and quercetin, the major flavonoids presented in the chamomile flower, are abundant in vegetables, fruits and red wine.³¹ Chamomile is one of the richest natural sources of apigenin. Apigenin not only has low toxicity but also shows antitumor activities by modulating multiple signaling pathways. Apigenin can sensitize cancer cells to paclitaxel-induced apoptosis through suppressing superoxide dismutase activity, which then leads to accumulation of ROS and cleavage of caspase-2.³⁰ It has been suggested that the combined use of apigenin and paclitaxel is an effective way to decrease the dose of paclitaxel taken.³⁰ Quercetin is beneficial in the treatment of sciatic ischemia-reperfusion injury because of its anti-apoptotic and anti-inflammatory effects and its ability to decrease the expression of NF- κ B.³² The oxaliplatin-related neurotoxic effect appears to occur at least partially through oxidative stress-induced damage in dorsal horn neurons, reflected by lipid peroxidation and protein nitrosylation.³³ Lipid peroxidation and tyrosine nitrosylation are prevented by quercetin treatment by inhibiting iNOS expression in the dorsal horn region.³³ Quercetin is also reported to ameliorate paclitaxel-induced neuropathic pain by stabilizing mast cells and subsequently blocking PKC ϵ -dependent activation of TRPV1.³⁴

4.4. Ginkgo biloba L

Ginkgo biloba extract is among the most widely-sold herbal dietary supplements in the United States. Its biological effects include scavenging free radicals, lowering oxidative stress, reducing neural damage, reducing platelet aggregation, anti-inflammation, anti-tumor activities, and anti-aging.³⁵ *Ginkgo biloba* extract has been shown to attenuate hyperalgesia and to prevent neural deterioration in rat models of chemotherapy-induced peripheral neuropathy.^{36, 37} EGb-761 is extracted from the leaves of *Ginkgo biloba* and has analgesic and anti-inflammatory properties.³⁸ EGb-761 can attenuate thermal hyperalgesia and mechanical allodynia dose-dependently on neuropathic pain in mice.³⁸ EGb-761 treatment significantly decreases pro-inflammatory

cytokines and enhances mu opioid receptor (MOR) expression in the sciatic nerve with chronic constriction injury.³⁸ Oxidative stress after cisplatin administration significantly increases nitric oxide (NO) and glutathione (GSH) levels, but decreases malondialdehyde (MDA) levels in brain tissue in rats.³⁹ EGb-761 can reverse the effects of cisplatin on NO and GSH levels without affecting the decreased MDA levels. EGb-761, having antioxidant properties, may improve the oxidative stress-related neurological side effects of cisplatin.³⁹

4.5. *Salvia officinalis* L

Salvia officinalis (Sage) is a plant in the family of Lamiaceae. In the folk medicines of Asia and Latin America, it has been used for the treatment of different kinds of disorders, including seizures, ulcers, gout, rheumatism, inflammation, dizziness, tremor, paralysis, diarrhea, and hyperglycemia. A previous review reported that *Salvia officinalis* has anticancer, anti-inflammatory, antinociceptive, and antioxidant effects, which can protect cells against ROS over-production and therefore can counteract oxidative stress-mediated tissue damage.⁴⁰ *Salvia officinalis* has been shown to have analgesic and anti-inflammatory effects in a rat model of vincristine-induced peripheral neuropathy, suggesting that it could be useful in the treatment of chemotherapy-induced peripheral neuropathic pain.⁴¹ Moreover, *salvia officinalis* extracts have been shown to protect against oxidative and alkylation damage to DNA in human HCT15 and CO115 cells (in two colon cell lines).⁴² The main flavonoids isolated from *Salvia officinalis* include apigenin, quercetin, and rosmarinic acid.⁴⁰ Rosmarinic acid, one of the most abundant flavonoids in *Salvia officinalis* extracts, has been extensively studied for its anticancer, antioxidant, anti-inflammatory, antinociceptive, cognitive, and memory-enhancing effects.⁴⁰ A recent study found that Rosmarinic acid had potential for the management of oxaliplatin-induced peripheral neuropathy due to the therapeutic activity against oxaliplatin-induced mitochondrial dysfunction and neuroinflammation.⁴³

4.6. *Fritillaria species*

Fritillaria is a genus of bulbous plants in the family Liliaceae. It is known as Bei-Mu in traditional Chinese medicine (TCM). In TCM theory, *fritillaria* is claimed to promote the lung's dispersing function, resolving phlegm, relieving cough, and detoxicating and dissolving lumps and masses. Over 130 identified compounds have been isolated from *Fritillaria*, and about 86% of these have an isosteroidal alkaloid skeleton, including Peimine (verticine) and Peiminine (verticinone).⁴⁴ The alkaloid verticinone exerts a good antinociceptive effect on inflammatory pain and paclitaxel-induced neuropathic pain, probably through both peripheral and central mechanisms, and it might be partly involved in some sedation effects.⁴⁵ Verticinone can dose-dependently inhibit nitric oxide production and also suppress inducible nitric oxide synthase and COX-2 expression in lipopolysaccharide-stimulated RAW 264.7 macrophages.⁴⁶ Verticinone can also suppress the production of pro-inflammatory cytokines such as tumor necrosis factor- α and interleukin-1 β in a dose-dependent manner, along with inhibiting the NF- κ B signaling pathway.⁴⁶ Moreover, peimine exhibits anti-inflammatory and pain suppression properties by blocking the sodium ion channel (Nav1.7) and inhibiting the potassium ion channel (Kv1.3).⁴⁷

4.7. *Curcuma longa* L

Curcuma longa (also known as Turmeric) is a rhizomatous perennial

herb in the family Zingiberaceae. Curcumin is the principal curcuminoid of *Curcuma longa*. Curcumin has been found recently to have antioxidant, anti-inflammatory, and anticancer effects and has been extensively used as a neuroprotective agent to reduce oxidative damage in neurodegenerative disorders.⁴⁸ Curcumin is reported to accelerate the repair of sciatic nerve injury in rats through reducing Schwann cell apoptosis and promoting myelination.⁴⁹ Peripheral nerve injury induces long-lasting changes in pain related molecules in the spinal cord and thus mainly accounts for the central mechanisms underlying neuropathic pain. BDNF and COX-2 are well-documented pro-nociceptive molecules that are expressed in the spinal dorsal horn after peripheral nerve injury.⁵⁰ Curcumin exerts a therapeutic role in neuropathic pain by down-regulating p300/CREB-binding protein histone acetyltransferase activity mediated gene expression of BDNF and COX-2.⁵⁰ Curcumin also reduces the histological changes induced by oxaliplatin and cisplatin in the sciatic nerve with reduction in nerve fiber caliber and areas of demyelination.⁵¹ The combination of curcumin with anti-neoplastic agents such as cisplatin, paclitaxel, and 5-fluorouracil may result in synergistic antitumor activity in various cancers and reduce the toxicity associated with the use of drugs.^{52,53}

4.8. *Angelica dahurica* (Fisch.ex Hoffm)

Angelicae Dahuricae (also known as Bai Zhi) has long been used for the treatment of headache, rhinitis, and colds in traditional Chinese medicine. *Angelicae dahuricae* is known to have anti-inflammatory, analgesic, and antipyretic actions. It inhibits lipopolysaccharide-induced NO, TNF- α and PGE2 production, as well as iNOS and COX-2 expression in macrophages through blockade of the phosphorylation of MAPKs, following I- κ B α degradation and NF- κ B activation.⁵⁴ Auraptenol is a phytochemical isolated from *Angelicae dahurica*. In a rat model of vincristine-induced neuropathic pain, auraptenol demonstrated excellent analgesic activity through serotonin 5-HT1A receptors, with no apparent adverse effects.⁵⁵

4.9. *Camellia sinensis* L

Green tea is a type of tea that is made from *Camellia sinensis* leaves that have not undergone the same withering and oxidation process used to make oolong teas and black teas. Green tea extracts are known to be a useful adjuvant to alleviate sensory symptoms in a rat model of oxaliplatin-induced peripheral neuropathy.⁵⁶ The most abundant active component of green tea is epigallocatechin-3-gallate (EGCG), which has antioxidant, anti-inflammatory, and antitumor-progression properties. EGCG is able to modulate different types of neuropathic pain by downregulating the expression levels of NF- κ B, JNKs, nNOS/NO, CX3CL1, and TNF- α protein.⁵⁷ EGCG has also been associated with cancer prevention and treatment. The additive and synergistic effects of EGCG when combined with conventional cancer therapies have been proposed, and its anti-inflammatory and antioxidant activities have been related to amelioration of cancer therapy side effects.⁵⁸

4.10. *Ocimum sanctum* L

Ocimum sanctum L. or *Ocimum tenuiflorum* L., also known as Holy Basil or Tulsi, is an important medicinal plant in the various traditional and folk systems of medicine in Southeast Asia. *Ocimum sanctum*, including the leaves, stem, root, flowers, and seeds, have numerous biological and pharmacological activities, including antioxidant, anti-inflammatory, antiallergic, immunomodulatory, antimicrobial, antistress,

Table 2
Chinese herbal formulas for treatment of chemotherapy-induced peripheral neuropathy.

| Formula (ingredient) | Action | Chemotherapy drug (study type) | Effects |
|--|--|--|---|
| Shao Yao Gan Cao Tang (Rx. <i>Paeoniae Alba</i> , Rx. <i>Glycyrrhizae Preparata</i>) | Softens the Liver, nourishes the Yin-Blood, moderates painful spasms, relieves pain, harmonizes the Middle Jiao, replenishes Body Fluids | Paclitaxel (rat study) paclitaxel and carboplatin combinations (clinical study) | Attenuate hyperalgesia and allodynia ⁶⁶ Reduce and prevent arthralgia and myalgia, ^{67,68} |
| Gui Zhi Jia Shu Fu Tang (Ram. <i>Cinnamomi</i> , Rx. <i>Paeoniae Alba</i> , Fr. <i>Jujube</i> , Rz. <i>Zingiberis Recens</i> , Rx. <i>Glycyrrhizae</i> , Rz. <i>Atractylodis</i> , Rx. <i>Aconiti Lateralis Preparata</i>) | Expels Wind and Dampness, invigorates the Blood, promotes urination | Oxaliplatin (rat study) FOLFOX regimen (clinical study) | Decrease spinal glial activation, IL-1 β , and TNF- α in the spinal cord ⁶⁹ Reduction in neuropathy evaluated with neurotoxicity criteria (Debiopharm) ⁷⁰ |
| Ji Sheng Shen Qi Wan (Rx. <i>Rehmanniae Preparata</i> , Fr. <i>Corni</i> , Rx. <i>Dioscoreae</i> , Rz. <i>Alismatis</i> , <i>Poria</i> , Cx. <i>Moutan</i> , Cx. <i>Cinnamomi</i> , Rx. <i>Aconiti Lateralis Preparata</i> , Rx. <i>Cyathulae</i> , Sm. <i>Plantaginis</i>) | Warms Yang, tonifies the Kidneys, aids water transformation, promotes urination, reduces edema | Oxaliplatin and paclitaxel (rat study) Bortezomib (rat study) Various agents in clinical studies | Decrease ROS, TNF- α , TRPV4, TRPA1 and TRPM8 expression ⁷¹ Decrease allodynia ⁷² Controversial results ⁷³ |

analgesic, antipyretic, antihypertensive, antidiabetic, cardioprotective, gastroprotective, hepatoprotective, renoprotective, radioprotective, chemopreventive, and anticancer properties.⁵⁹ It can attenuate chronic constriction injury- and vincristine-induced neuropathic pain as well as decrease the oxidative stress and calcium levels in rats.^{60,61} Apigenin, rosmarinic acid, and eugenol, some of the phenolic compounds present in *Ocimum sanctum*,⁶² have been shown to have antinociceptive and anti-inflammatory activities that may either improve neuropathic pain or prevent nerve damage.^{63–65}

4.11. Herbal formulas

Herbal formulas are typically combinations of several herbs used to treat various diseases or symptoms according to the theory of traditional Chinese medicine. They are also commonly used in traditional Japanese (Kampo) and Korean medicine. The herbal formulas have different names in different countries, leading to confusion among readers. Three Chinese herbal formulas commonly used for the treatment of CIPN are Shao Yao Gan Cao Tang (芍藥甘草湯), Gui Zhi Jia Shu Fu Tang (桂枝加朮附湯), and Ji Sheng Shen Qi Wan (濟生腎氣丸) (Table 2). Shao Yao Gan Cao Tang, also called Shakuyakukanzoto (in Japanese) and Jakyakgamcho-Tang (in Korean), is an herbal mixture of *Paeoniae radix* and *Glycyrrhizae radix*. It remarkably attenuated hyperalgesia and allodynia in a rat model of paclitaxel-induced neuropathic pain.⁶⁶ It was also effective in reducing arthralgia and myalgia occurring in paclitaxel and carboplatin combinations of chemotherapy in a small retrospective case analysis.⁶⁷ In addition, prophylactic administration of Shao Yao Gan Cao Tang is effective against paclitaxel- and carboplatin-induced myalgia and arthralgia.⁶⁸ Gui Zhi Jia Shu Fu Tang, also called Keishikajutsu (in Japanese) and Gyejjigachulbu-Tang (in Korean), contains *Aconiti tuber*, *Atractylodis lanceae rhizome*, *Cinnamomi cortex*, *Glycyrrhizae radix*, *Paeoniae radix*, *Zingiberis rhizome*, and *Zizyphi fructus*. It alleviates oxaliplatin-induced neuropathic pain in rats by suppressing spinal glial activation and pro-inflammatory cytokines, IL-1 β and TNF- α , in the spinal cord.⁶⁹ In addition, it is effective against FOLFOX regimen induced neuropathy in patients with metastatic colorectal cancer.⁷⁰ Ji Sheng Shen Qi Wan, also called Niu Che Sen Qi Wan (牛車腎氣丸), Goshajinkigan (in Japanese), and Jesengsingi-Hwan (in Korean), contains *Achyranthis bidentatae radix*, *Alismatis rhizome*, *Aconiti*

tuber, *Cinnamomi cortex*, *Corni fructus*, *Dioscorea opposita rhizoma*, *Plantaginis semen*, *Poria alba*, *Moutan cortex*, and *Rehmannia viride radix*. It ameliorated oxaliplatin- and paclitaxel-induced neuropathic pain in a rat model by suppressing ROSs, TNF- α , TRPV4, TRPA1, and TRPM8 expression.⁷¹ It also reduces bortezomib-induced mechanical allodynia in rats.⁷² However, the results of clinical studies on the preventive effects of Ji Sheng Shen Qi Wan on CIPN are still controversial.⁷³

5. Conclusion

Therapeutic choices for patients with CIPN are limited, and prevention or management requires an understanding of the neuropathy pathophysiology (Fig. 1). Despite the debilitating symptoms of chemotherapy-induced PN, there exists no truly effective treatment strategy capable of preventing or managing the associated nerve damage. Therapies based on complementary therapies have been reported to improve the symptoms of CIPN. Some novel attempts using acupuncture, reflexology,⁷⁴ and sensorimotor training⁷⁵ have now revealed promising results. CIPN, having varied pathobiology, presents many molecular mechanisms that can be targeted with complementary therapies. However, the absence of rigorous scientific design has impeded the use of complementary therapies in mainstream medicine. The current study analyzed 10 commonly used medicinal herbs for their antioxidant capacity in the rat models. The focus of this review is on medicinal plants with respect to their anti-oxidative effects for complementary treatment of CIPN. From the description of the suggested effect mechanisms of the different medicinal plants, it should be clear that these plants have many other effective mechanisms; it has not been determined whether the anti-oxidative effect is the major mechanism against CIPN. Some experimental evidence has indicated that either monastrol or taxol could be active in post-mitotic neurons, possibly through mediation of transcriptional regulation in axon growth and regeneration.^{76,77} Further studies are required to optimize the use of these novel agents to alleviate the distressing symptoms of neuropathy and brought them to clinical practice. We still have much to learn about complementary therapies in terms of their efficacy, safety, and cost-effectiveness. To prevent or reduce chemotherapy-induced PN, a truly collaborative effort between practitioners of complementary therapies, conventional physicians, and research scientists is needed.

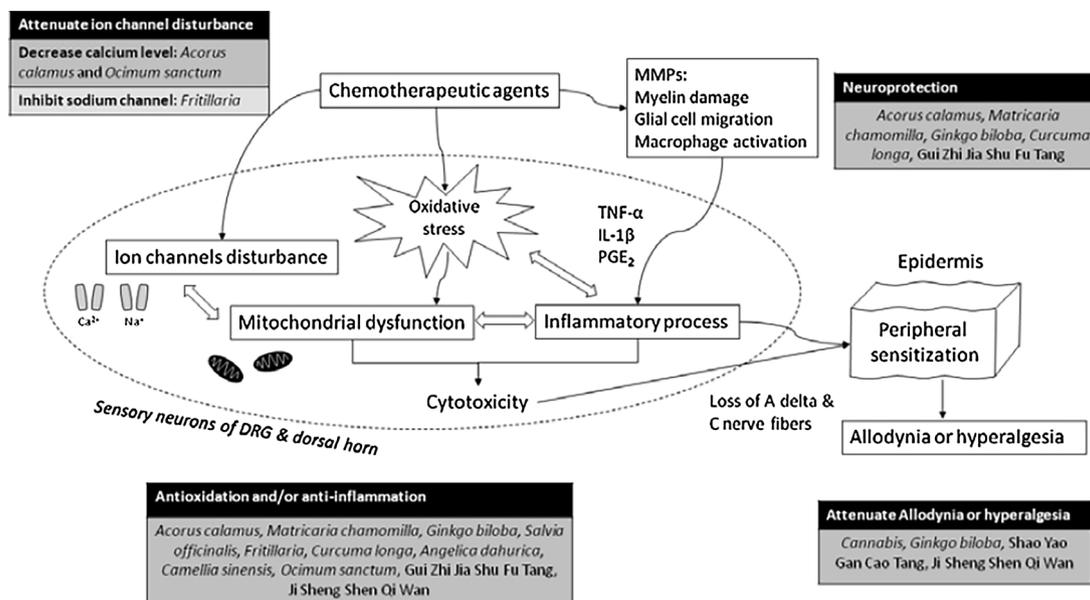


Fig. 1. A proposed diagram of the therapeutic network medicinal plants for chemotherapy.

Data availability

Data underlying this research will be sent by email to the publisher and are available from the corresponding author upon request.

Author disclosure statement

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References

- Addington EL, Sohl SJ, Tooze JA, Danhauer SC. Convenient and Live Movement (CALM) for women undergoing breast cancer treatment: challenges and recommendations for internet-based yoga research. *Complement Ther Med*. 2018;37(April):77–79.
- Bozcuk H, Ozcan K, Erdogan C, et al. A comparative study of art therapy in cancer patients receiving chemotherapy and improvement in quality of life by watercolor painting. *Complement Ther Med*. 2017;30(February):67–72.
- Doorenbos AZ, Berger AM, Brohard-Holbert C, et al. ONS research priorities survey. *Oncol Nurs Forum*. 2008;35(November 6):E100–E107.
- Wolf S, Barton D, Kottschade L, et al. Chemotherapy-induced peripheral neuropathy: Prevention and treatment strategies. *Eur J Cancer*. 2008;44(July 11):1507–1515.
- Boyette-Davis JA, Walters ET, Dougherty PM. Mechanisms involved in the development of chemotherapy-induced neuropathy. *Pain Manag*. 2015;5(4):285–296.
- Seretny M, Currie GL, Sena ES, et al. Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: a systematic review and meta-analysis. *Pain*. 2014;155(December 12):2461–2470.
- Hile ES, Fitzgerald GK, Studenski SA. Persistent mobility disability after neurotoxic chemotherapy. *Phys Ther*. 2010;90(November 11):1649–1657.
- Menorca RM, Fussell TS, Elfar JC. Nerve physiology: mechanisms of injury and recovery. *Hand Clin*. 2013;29(August (3)):317–330.
- Azhary H, Farooq MU, Bhanushali M, et al. Peripheral neuropathy: differential diagnosis and management. *Am Fam Physician*. 2010;81(April (7)):887–892.
- Fukuda Y, Li Y, Segal RA. A mechanistic understanding of axon degeneration in

- chemotherapy-induced peripheral neuropathy. *Front Neurosci*. 2017;11:481.
- Weimer LH. Medication-induced peripheral neuropathy. *Curr Neurol Neurosci Rep*. 2003;3(January 1):86–92.
- Areti A, Yerra VG, Naidu V, Kumar A. Oxidative stress and nerve damage: role in chemotherapy induced peripheral neuropathy. *Redox Biol*. 2014;2:289–295.
- Wang XM, Lehky TJ, Brell JM, Dorsey SG. Discovering cytokines as targets for chemotherapy-induced painful peripheral neuropathy. *Cytokine*. 2012;59(July 1):3–9.
- Jordan MA, Wilson L. Microtubules as a target for anticancer drugs. *Nat Rev Cancer*. 2004;4(April (4)):253–265.
- Grisold W, Cavaletti G, Windebank AJ. Peripheral neuropathies from chemotherapeutics and targeted agents: diagnosis, treatment, and prevention. *Neuro Oncol*. 2012;14(Suppl. 4 (September)):iv45–iv54.
- Han Y, Smith MT. Pathobiology of cancer chemotherapy-induced peripheral neuropathy (CIPN). *Front Pharmacol*. 2013;4(December):156.
- Salvemini D, Little JW, Doyle T, Neumann WL. Roles of reactive oxygen and nitrogen species in pain. *Free Radic Biol Med*. 2011;51(September (5)):951–966.
- McDonald ES, Windebank AJ. Cisplatin-induced apoptosis of DRG neurons involves bax redistribution and cytochrome c release but not fas receptor signaling. *Neurobiol Dis*. 2002;9(March (2)):220–233.
- Ta LE, Schmelzer JD, Bieber AJ, et al. A novel and selective poly (ADP-ribose) polymerase inhibitor ameliorates chemotherapy-induced painful neuropathy. *PLoS One*. 2013;8(1):e54161.
- Cavaletti G. Chemotherapy-induced peripheral neurotoxicity (CIPN): What we need and what we know. *J Peripher Nerv Syst*. 2014;19(June (2)):66–76.
- Muthuraman A, Singh N. Attenuating effect of hydroalcoholic extract of Acorus calamus in vincristine-induced painful neuropathy in rats. *J Nat Med*. 2011;65(July (3-4)):480–487.
- Devaki M, Nirupama R, Nirupama M, Yajurvedi HN. Protective effect of rhizome extracts of the herb, vacha (Acorus calamus) against oxidative damage: An in vivo and in vitro study. *Food Sci Hum Wellness*. 2016;5(2):76–84 2016/06/01/.
- Abrams DI. Integrating cannabis into clinical cancer care. *Curr Oncol*. 2016;23(March (2)):S8–S14.
- Deng L, Guindon J, Vemuri VK, et al. The maintenance of cisplatin- and paclitaxel-induced mechanical and cold allodynia is suppressed by cannabinoid CB2 receptor activation and independent of CXCR4 signaling in models of chemotherapy-induced peripheral neuropathy. *Mol Pain*. 2012;8(September):71.
- Rahn EJ, Makriyannis A, Hohmann AG. Activation of cannabinoid CB1 and CB2 receptors suppresses neuropathic nociception evoked by the chemotherapeutic agent vincristine in rats. *Br J Pharmacol*. 2007;152(November (5)):765–777.
- Rahn EJ, Deng L, Thakur GA, et al. Prophylactic cannabinoid administration blocks the development of paclitaxel-induced neuropathic nociception during analgesic treatment and following cessation of drug delivery. *Mol Pain*. 2014;10(April):27.
- Deng L, Guindon J, Cornett BL, et al. Chronic cannabinoid receptor 2 activation reverses paclitaxel neuropathy without tolerance or cannabinoid receptor 1-dependent withdrawal. *Biol Psychiatry*. 2015;77(March (5)):475–487.
- McKay DL, Blumberg JB. A review of the bioactivity and potential health benefits of chamomile tea (Matricaria recutita L.). *Phytother Res*. 2006;20(July (7)):519–530.
- Srivastava JK, Pandey M, Chamomile Gupta S. A novel and selective COX-2 inhibitor with anti-inflammatory activity. *Life Sci*. 2009;85(November (19-20)):663–669.
- Xu Y, Xin Y, Diao Y, et al. Synergistic effects of apigenin and paclitaxel on apoptosis of cancer cells. *PLoS One*. 2011;6(12):e29169.
- McKay DL, Blumberg JB. A review of the bioactivity and potential health benefits of peppermint tea (Mentha piperita L.). *Phytother Res*. 2006;20(August (8)):619–633.
- Gholami M, Khayat ZK, Anbari K, et al. Quercetin ameliorates peripheral nerve

- ischemia-reperfusion injury through the NF-kappa B pathway. *Anat Sci Int*. 2017;92(June (3)):330–337.
33. Azevedo MI, Pereira AF, Nogueira RB, et al. The antioxidant effects of the flavonoids rutin and quercetin inhibit oxaliplatin-induced chronic painful peripheral neuropathy. *Mol Pain*. 2013;9(October):53.
 34. Gao W, Zan Y, Wang ZJ, et al. Quercetin ameliorates paclitaxel-induced neuropathic pain by stabilizing mast cells, and subsequently blocking PKCepsilon-dependent activation of TRPV1. *Acta Pharmacol Sin*. 2016;37(September (9)):1166–1177.
 35. Chan PC, Xia Q, Fu PP. Ginkgo biloba leave extract: Biological, medicinal, and toxicological effects. *J Environ Sci Health C Environ Carcinog Ecotoxicol Rev*. 2007;25(July-September (3)):211–244.
 36. Ozturk G, Anlar O, Erdogan E, et al. The effect of Ginkgo extract EGb761 in cisplatin-induced peripheral neuropathy in mice. *Toxicol Appl Pharmacol*. 2004;196(April (1)):169–175.
 37. Park HJ, Lee HG, Kim YS, et al. Ginkgo biloba extract attenuates hyperalgesia in a rat model of vincristine-induced peripheral neuropathy. *Anesth Analg*. 2012;115(November (5)):1228–1233.
 38. Zhu C, Li W, Xu F, et al. Effects of Ginkgo biloba extract EGb-761 on neuropathic pain in mice: involvement of opioid system. *Phytother Res*. 2016;30(November (11)):1809–1816.
 39. Aydin D, Peker EG, Karakurt MD, et al. Effects of Ginkgo biloba extract on brain oxidative condition after cisplatin exposure. *Clin Invest Med*. 2016;39(December (6)):27511.
 40. Ghorbani A, Esmaeilzadeh M. Pharmacological properties of *Salvia officinalis* and its components. *J Tradit Complement Med*. 2017;7(October (4)):433–440.
 41. Abad ANA, Nouri MHK, Tavakkoli F. Effect of *Salvia officinalis* hydroalcoholic extract on vincristine-induced neuropathy in mice. *Chin J Nat Med*. 2011;9(5):354–358 2011/09/01/.
 42. Ramos AA, Pedro D, Collins AR, Pereira-Wilson C. Protection by *Salvia* extracts against oxidative and alkylation damage to DNA in human HCT15 and CO115 cells. *J Toxicol Environ Health A*. 2012;75(13-15):765–775.
 43. Areti A, Komirishetty P, Kalvala AK, et al. Rosmarinic acid mitigates mitochondrial dysfunction and spinal glial activation in oxaliplatin-induced peripheral neuropathy. *Mol Neurobiol*. 2018(February).
 44. Li HJ, Jiang Y, Li P. Chemistry, bioactivity and geographical diversity of steroidal alkaloids from the Liliaceae family. *Nat Prod Rep*. 2006;23(October (5)):735–752.
 45. Xu F, Xu S, Wang L, et al. Antinociceptive efficacy of verticinone in murine models of inflammatory pain and paclitaxel induced neuropathic pain. *Biol Pharm Bull*. 2011;34(9):1377–1382.
 46. Wu K, Mo C, Xiao H, et al. Imperialine and verticinone from bulbs of *Fritillaria wabuensis* inhibit pro-inflammatory mediators in LPS-stimulated RAW 264.7 macrophages. *Planta Med*. 2015;81(July (10)):821–829.
 47. Xu J, Zhao W, Pan L, et al. Peimine, a main active ingredient of *Fritillaria*, exhibits anti-inflammatory and pain suppression properties at the cellular level. *Fitoterapia*. 2016;111:1–6 2016/06/01/.
 48. Prasad S, Gupta SC, Tyagi AK, Aggarwal BB. Curcumin, a component of golden spice: from bedside to bench and back. *Biotechnol Adv*. 2014;32(November (6)):1053–1064.
 49. Zhao Z, Li X, Li Q. Curcumin accelerates the repair of sciatic nerve injury in rats through reducing Schwann cells apoptosis and promoting myelination. *Biomed Pharmacother*. 2017;92(August):1103–1110.
 50. Zhu X, Li Q, Chang R, et al. Curcumin alleviates neuropathic pain by inhibiting p300/CBP histone acetyltransferase activity-regulated expression of BDNF and cox-2 in a rat model. *PLoS One*. 2014;9(3):e91303.
 51. Al Moundhri MS, Al-Salam S, Al Mahrouqee A, et al. The effect of curcumin on oxaliplatin and cisplatin neurotoxicity in rats: some behavioral, biochemical, and histopathological studies. *J Med Toxicol*. 2013;9(March (1)):25–33.
 52. Quispe-Soto ET, Calaf GM. Effect of curcumin and paclitaxel on breast carcinogenesis. *Int J Oncol*. 2016;49(December (6)):2569–2577.
 53. Mendonca LM, da Silva Machado C, Teixeira CC, et al. Curcumin reduces cisplatin-induced neurotoxicity in NGF-differentiated PC12 cells. *Neurotoxicology*. 2013;34(January):205–211.
 54. Kang OH, Lee GH, Choi HJ, et al. Ethyl acetate extract from *Angelica dahuricae* Radix inhibits lipopolysaccharide-induced production of nitric oxide, prostaglandin E2 and tumor necrosis factor-alpha via mitogen-activated protein kinases and nuclear factor-kappaB in macrophages. *Pharmacol Res*. 2007;55(April (4)):263–270.
 55. Wang Y, Cao SE, Tian J, et al. Auraptinol attenuates vincristine-induced mechanical hyperalgesia through serotonin 5-HT1A receptors. *Sci Rep*. 2013;3(November):3377.
 56. Lee JS, Kim YT, Jeon EK, et al. Effect of green tea extracts on oxaliplatin-induced peripheral neuropathy in rats. *BMC Complement Altern Med*. 2012;12(August):124.
 57. Bimonte S, Cascella M, Schiavone V, et al. The roles of epigallocatechin-3-gallate in the treatment of neuropathic pain: an update on preclinical in vivo studies and future perspectives. *Drug Des Devel Ther*. 2017;11:2737–2742.
 58. Lecumberri E, Dupertuis YM, Miralbell R, Pichard C. Green tea polyphenol epigallocatechin-3-gallate (EGCG) as adjuvant in cancer therapy. *Clin Nutr*. 2013;32(December (6)):894–903.
 59. Bhattacharyya P, Bishayee A. *Ocimum sanctum* Linn. (Tulsi): an ethnomedicinal plant for the prevention and treatment of cancer. *Anticancer Drugs*. 2013;24(August (7)):659–666.
 60. Kaur G, Bali A, Singh N, Jaggi AS. Ameliorative potential of *Ocimum sanctum* in chronic constriction injury-induced neuropathic pain in rats. *An Acad Bras Cienc*. 2015;87(March (1)):417–429.
 61. Kaur G, Jaggi AS, Singh N. Exploring the potential effect of *Ocimum sanctum* in vincristine-induced neuropathic pain in rats. *J Brachial Plex Peripher Nerve Inj*. 2010;5(January):3.
 62. Baliga MS, Jimmy R, Thilakchand KR, et al. *Ocimum sanctum* L (Holy Basil or Tulsi) and its phytochemicals in the prevention and treatment of cancer. *Nutr Cancer*. 2013;65(Suppl. 1):26–35.
 63. El Shoubaky GA, Abdel-Daim MM, Mansour MH, Salem EA. Isolation and identification of a flavone apigenin from marine red alga *Acanthophora specifera* with antinociceptive and anti-inflammatory activities. *J Exp Neurosci*. 2016;10:21–29.
 64. Ghasemzadeh Rahbardar M, Amin B, Mehri S, et al. Anti-inflammatory effects of ethanolic extract of *Rosmarinus officinalis* L. and rosmarinic acid in a rat model of neuropathic pain. *Biomed Pharmacother*. 2017;86(February):441–449.
 65. Paula-Freire LI, Molska GR, Andersen ML, Carlini EL. *Ocimum gratissimum* essential oil and its isolated compounds (Eugenol and myrcene) reduce neuropathic pain in mice. *Planta Med*. 2016;82(February (3)):211–216.
 66. Hidaka T, Shima T, Nagira K, et al. Herbal medicine *Shakuyaku-kanzo*-to reduces paclitaxel-induced painful peripheral neuropathy in mice. *Eur J Pain*. 2009;13(January (1)):22–27.
 67. Fujii K, Okamoto S, Saitoh K, et al. [The efficacy of *Shakuyaku-Kanzo-to* for peripheral nerve dysfunction in paclitaxel combination chemotherapy for epithelial ovarian carcinoma]. *Gan To Kagaku Ryoho*. 2004;31(October (10)):1537–1540.
 68. Yoshida T, Sawa T, Ishiguro T, et al. The efficacy of prophylactic *Shakuyaku-Kanzo-to* for myalgia and arthralgia following carboplatin and paclitaxel combination chemotherapy for non-small cell lung cancer. *Support Care Cancer*. 2009;17(March (3)):315–320.
 69. Jung Y, Lee JH, Kim W, et al. Anti-allodynic effect of *Buja* in a rat model of oxaliplatin-induced peripheral neuropathy via spinal astrocytes and pro-inflammatory cytokines suppression. *BMC Complement Altern Med*. 2017;17(January (1)):48.
 70. Yamada T, Kan H, Matsumoto S, et al. [Reduction in oxaliplatin-related neurotoxicity by the administration of *Keishikajutsu-buto* (TJ-18) and powdered processed aconite root]. *Gan To Kagaku Ryoho*. 2012;39(November (11)):1687–1691.
 71. Cascella M, Muzio MR. Potential application of the *Kampo* medicine *goshajinkigan* for prevention of chemotherapy-induced peripheral neuropathy. *J Integr Med*. 2017;15(March (2)):77–87.
 72. Higuchi H, Yamamoto S, Ushio S, et al. *Goshajinkigan* reduces bortezomib-induced mechanical allodynia in rats: Possible involvement of kappa opioid receptor. *J Pharmacol Sci*. 2015;129(November (3)):196–199.
 73. Kuriyama A, Endo K. *Goshajinkigan* for prevention of chemotherapy-induced peripheral neuropathy: a systematic review and meta-analysis. *Support Care Cancer*. 2018;26(April (4)):1051–1059.
 74. Ben-Horin I, Kahan P, Ryvo L, et al. Acupuncture and reflexology for chemotherapy-induced peripheral neuropathy in breast Cancer. *Integr Cancer Ther*. 2017;16(September (3)):258–262.
 75. Streckmann F, Kneis S, Leifert JA, et al. Exercise program improves therapy-related side-effects and quality of life in lymphoma patients undergoing therapy. *Ann Oncol*. 2014;25(February (2)):493–499.
 76. Hsu ST, Yao CH, Hsu YM, et al. Effects of taxol on regeneration in a rat sciatic nerve transection model. *Sci Rep*. 2017;7(February):42280.
 77. Nadar VC, Ketschek A, Myers KA, et al. Kinesin-5 is essential for growth-cone turning. *Curr Biol*. 2008;18(December (24)):1972–1977.