Herbal Medicines as Adjuncts to Cancer Chemotherapy—Part 2: Non-Immune Support

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Abstract

Part 1 of this article focused on immunomodulating herbal adjuncts to chemotherapy treatment. Part 2 highlights herbal therapies for specific adverse side effects, including nausea, vomiting, anorexia, mucositis, neuropathy, and organ damage. Various herbal formulas are examined, including Liù Jūn Zǐ Tāng (Six Gentlemen Decoction, rikkunshi-tō), Niú Chē Shèn Qì Wán (Life Preserving Kidney Qi Pill, goshajinkigan), Guilongtongluofang, Sháo yào gān cǎo tāng (Peony and Licorice Decoction, shakuyaku-kanzo-tō), and others. Individual herbs examined in depth include *Astragalus membranaceus* (astragalus), *Zingiber officinale* (ginger), *Cannabis sativa* (cannabis), *Achillea millefolium* (yarrow), *Plantago* spp. (plantain), *Glycyrrhiza* spp. (licorice), *Matricaria chamomilla* (chamomile), *Mentha* x *piperita* (peppermint), *Rhodiola rosea* (rose root), *Rhodiola algida* (Tibetan rose root), *Annona muricata* (soursop), *Silybum marianum* (milk thistle), capsaicin, honey, and *Taiwanofungus camphoratus* (stout camphor fungus). The findings discussed in this paper present promising results for herbal therapeutic remedies to treat the diverse adverse side effects affecting quality of life associated with cancer treatment effectively.

Keywords: herbal medicine, chemotherapy, cancer, mucositis, nausea, neuropathy

Introduction

Chemotherapy remains a mainstay of the conventional approach to many types of cancer. Chemotherapy agents, even effective ones, nearly always come with a plethora of adverse side effects that greatly diminish quality of life (QoL), some causing permanent damage or even causing risk to life. Part 1 of this article discussed immunomodulating herbs as a valuable addition to cancer treatment. In part 2, a diverse set of herbs and herbal formulas are discussed in the treatment of complications of chemotherapy, including nausea, vomiting, anorexia, mucositis, neuropathy, and organ damage, with the hope of improving overall QoL and, in some cases, improving the effectiveness of the chemotherapy agents.

Treatments for Nausea, Vomiting, and Anorexia

Nausea and vomiting are very common side effects of chemotherapy treatments for cancer. Chemotherapy-induced nausea and vomiting (CINV) is categorized into three different types of nausea: anticipatory nausea that occurs before the start of chemotherapy, acute nausea that occurs within 24 hours post chemotherapy, and delayed nausea that occurs after 24 hours and up to five days post chemotherapy. Anticipatory nausea usually only develops if a patient suffers from acute or delayed nausea of sufficient severity, usually on multiple occasions. Delayed CINV often results in using so-called rescue medication, meaning additional agents on top of whatever was initially used to treat acute CINV. Rescue medication increases the risk for adverse effects and of course increases cost. All aspects of CINV must be addressed to eliminate the problem fully.

The typical drugs used to treat CINV are 5-HT_3 receptor antagonists such as ondansetron, granisetron, and dolasetron combined with a corticosteroid. Exact treatment programs may vary depending on the chemotherapy drug. The 5-HT_3 receptor antagonists are more effective against vomiting than they are against nausea, and despite medication, nausea and vomiting continue to be reported in $>70\%$ of chemotherapy patients.[1] The neurokinin-1 receptor antagonist drugs (NK1RA) aprepitant and rolapitant have been introduced more recently and are becoming more widely used for CINV, though currently they are expensive. One meta-analysis of nine trials found that adding a NK1RA to a 5-HT_3 receptor antagonist and dexamethasone resulted in no emesis in 75% of patients compared to 60% without the NK1RA—a significant improvement.[2] Hiccups, fatigue, and constipation are significantly more likely to occur in patients receiving NK1RA drugs than those who are not. More concerning is evidence from meta-analysis that these

drugs significantly increase the risk of severe infections compared to controls, without causing neutropenia.[3] Since 100% effectiveness has not been achieved with antiemetic drugs, and given their potentially serious adverse effects, there is still room for natural products in treating CINV.

Zingiber officinale (ginger) is a tropical and subtropical plant from the Zingiberaceae family. The rhizome of this plant has a long history of use in many conditions, most notably for nausea, vomiting, and a general upset stomach. A large ($n = 576$), multi-site clinical trial across the United States examined the effectiveness of ginger on acute CINV through dosing three ginger pills b.i.d. for six days, beginning three days before the start of chemotherapy, testing several doses of ginger.[4] This study found that all doses of ginger, including 0.5, 1.0, and 1.5 g, were effective at significantly reducing nausea (but not vomiting) on day 1 of chemotherapy. The largest improvement in nausea was seen with 0.5 and 1.0 g doses. The study also found that ginger supplementation prior to chemotherapy had a significant effect on anticipatory CIN, which thus resulted in reduced acute CIN. Ginger was safe and effective for CINV in one double-blind randomized trial in 57 Indian children undergoing chemotherapy.[5]

The most up-to-date meta-analysis of ginger for CINV also found it effective.[6] Based on a review of 10 randomized clinical trials, ginger was effective at reducing acute nausea and vomiting compared to placebo or standard care alone. This analysis actually found ginger most helpful for control of acute vomiting due to chemotherapy. Adding 1 g of encapsulated ginger (administered one hour before each chemotherapy treatment) to the protocol of most patients on emetogenic chemotherapy is a safe and effective way to augment the efficacy of standard anti-nausea drugs.

Liù Jūn Zǐ Tāng (Six Gentlemen Decoction) is a traditional Chinese herbal formula that originated in *Tài Píng Huì Mín Hé Jì Jú Fāng* (Formulary of the Pharmacy Service for Benefiting the People in the Taiping Era) by the Imperial Medical Bureau, published in 1107 CE. The formula has a long history of use in the treatment of patients with gastrointestinal disorders, particularly nausea and appetite loss. The Japanese name of this formula is rikkunshi-tō, and most modern research has been on this version of the formula, which adds two herbs to the original Six Gentlemen Decoction (see Table 1).

A clinical trial studied the effectiveness of rikkunshi-tō on body weight loss, nutritional parameters, and QoL after 48 weeks of 2.5 g/day, beginning four weeks after esophagectomy, in Japanese esophageal cancer patients. Significant results compared to control groups were found.[7] This study was small and non-randomized. However, it showed great promise, including the added effect of increased acyl ghrelin levels and an improvement in patient satisfaction of food consumption at 52 weeks postoperatively. Another similarly sized clinical trial had comparative positive results. It examined improvement in CINV and anorexia in patients with uterine cervical or corpus cancer receiving cisplatin and paclitaxel treatment through oral administration of rikkunshi-tō for 13 days compared to placebo.[8] This study found a significant improvement in the treatment group, with the added benefit of increased improvement over time, suggesting a cumulative effect. Another clinical trial on the efficacy of rikkunshi-tō in Japanese gastric cancer patients post gastrectomy found similar significant benefits in gastrointestinal symptoms and a significant increase in ghrelin concentration after a dose of 2.5 g t.i.d. for four weeks.[9] A clinical trial on rikkunshi-tō with Japanese patients undergoing cisplatin chemotherapy treatment for breast cancer found this granule preparation to be effective in the treatment of nausea and loss of appetite. This study used meal intake as the endpoint measure. Another small clinical trial found significant improvements in QoL, body weight, abdominal pain, acid reflux, diarrhea, and constipation, but no significant change in appetite or plasma ghrelin levels in post-gastrectomy gastric cancer patients when rikkunshi-tō was administered for four weeks, beginning six weeks after surgery.[10]

Cannabis sativa (cannabis) is an important medicine for CINV. It has been shown to act against acute and delayed phases of nausea and vomiting.[11] It has been shown to be effective for treating refractory CINV in two meta-analyses, though (−)-trans-Δ^9-tetrahydrocannabinol (THC or dronabinol), nabilone (a semi-synthetic THC analog), and THC-containing cannabis and its extracts are prone to causing euphoria (which some interpret negatively), dysphoria, somnolence, and dizziness

Table 1. Rikkunshi-Tō, a Modified Version of Liù Jūn Zǐ Tāng (Six Gentlemen Decoction)

Herb	Common names	Part used	Percent in formula	Notes
Atractylodes macrocephala	White atractylodes, bái zhú	Rhizome	19%	
Panax ginseng	Red ginseng, hóng shēn	Steamed root	19%	
Codonopsis pilosula	Codonopsis, dǎng shēn	Root	19%	Substitute for red ginseng
Pinellia ternata	Pinellia, zhì bàn xià	Processed tuber	19%	
Wolfiporia cocos	Hoelen, fú líng	Sclerotium	18%	
Citrus reticulata	Tangerine, chén pí	Aged peel	9%	
Glycyrrhiza uralensis	Asian licorice, zhì gān cǎo	Honey-fried root	5%	
Ziziphus jujuba	Jujube, dà zǎo	Fruit	9%	Not in original formula
Zingiber officinale	Ginger, gān jiāng	Dried rhizome	2%	Not in original formula

compared to prochlorperazine.[12,13] A different meta-analysis concluded there was only low-quality evidence that cannabinoids are effective for CINV.[14] Cannabidiol (CBD) also demonstrates antiemetic properties, in significant part via actions on serotonin receptors.[15] Higher serum levels of THC correlate with declining levels of emesis, with levels > 10 ng/mL leading to the greatest efficacy.[16] The usual dose of THC, either alone or in whole-plant extracts, is 2.5–20 mg q.d. up to q.i.d. Administration by inhalation is generally preferred for preventing acute nausea, as onset of effects is rapid. Oral doses are recommended simultaneously to prevent delayed emesis. For safety reasons, a vaporized product is preferred over a product that is smoked or isolates used in electronic pens. Patients with no or minimal prior exposure to THC should start with the lowest dose, and it should be raised slowly over time to mitigate adverse effects.

Astragalus membranaceus (astragalus, huáng qí) root is an immunomodulator with calming effects on the digestive system discussed in some depth in part 1 of this article. A sensitivity analysis of 27 randomized clinical trials of Chinese herbal medicine formulas found that astragalus was associated with reduced CINV.[17] In one such trial, 11 Chinese patients with advanced cancers undergoing chemotherapy and suffering anorexia as a result all took a herbal formula (see Table 2; notice similarities to the formula in Table 1) as a decoction in three daily doses 30 minutes after meals for three weeks.

Treatments for Mucositis

Mucositis, consisting of inflammation and ulceration of mucous membranes in the body (usually most notably in the mouth and pharynx, but potentially affecting the entire gut and other mucous membranes) is a frequent challenging side effect of chemotherapy for cancer. Mucositis is painful and can lead to difficulty eating and drinking, speaking, and communicating. It can also increase the risk of infections from open wounds. This can greatly impact a patient's QoL. Several natural and herbal remedies have been shown in clinical trials to provide helpful relief for this challenging side effect.

Achillea millefolium (yarrow) in the Asteraceae family has a long history of use around the world in many diverse cultures, particularly for skin and wound healing, as well as for its antibacterial, inflammation modulating, and styptic properties. A double-blind clinical trial examining yarrow mouthwash for mucositis showed a significant improvement in the severity of symptoms compared to the control group.[18] In this study, Iranian patients were instructed to hold 15 mL of yarrow distilled solution in their mouth for three minutes, gargle the solution, and then discard it, followed by strictly avoiding washing out their mouth or eating food for an hour. After 14 days there was significant improvement with yarrow compared to placebo; 71% of the participants who used yarrow had completely healed oral mucositis (OM) lesions.

Another inflammation-modulating member of the Asteraceae family, *Matricaria chamomilla* (chamomile), has also been extensively studied for helping patients with mucositis. Numerous clinical trials have been reported on chamomile related to exposure to a host of chemotherapy agents, as well as hematopoietic stem-cell transplants and radiation therapy. A meta-analysis of 11 clinical trials in humans found that chamomile products (mostly mouthwashes, but some using solutions that were primarily swallowed and not rinsed in the mouth) were effective at relieving mucositis.[19] Of 11 studies, 10 found chamomile was effective; one did not. Those studies that reported on adverse effects found there were none with chamomile.

Table 2. Chinese Herbal Formula for Chemotherapy Anorexia

Herb	Common names	Part used	Amount (daily dose)
Astragalus membranaceus	Astragalus, huáng qí	Root	24 g
Spatholobus suberectus	Spatholobus, jī xuè téng	Vine	16 g
Atractylodes macrocephala	White atractylodes, bái zhú	Rhizome	12 g
Wolfiporia cocos	Hoelen, fú líng	Sclerotium	12 g
Pinellia ternata	Pinellia, zhì bàn xià	Processed tuber	12 g
Citrus reticulata	Tangerine, chén pí	Aged peel	12 g
Alisma plantago-aquatica	Water plantain, zé xiè	Rhizome	12 g
Ziziphus jujuba	Jujube, dà zǎo	Fruit	12 g
Rhynchosia nulubilis	Black soy bean, lù huò	Fruit	12 g
Agastache rugosa	Licorice mint, tǔ può xiāng	Leaf, flower	8 g
Glycyrrhiza uralensis	Asian licorice, gān cǎo	Root	8 g
Plantago asiatica	Chinese plantain, chē qián zǐ	Seed	8 g
Crataegus pinnatifida	Japanese hawthorn, shān zhā	Fruit	8 g
Gallus gallus domesticus	Chicken gizzard lining, jī nèi jīn	Gizzard lining	8 g

Capsaicin, the potently spicy compound in *Capsicum annuum* (cayenne), when applied topically to skin mucus membrane tissues initially produces a burning sensation, but over time with repeated applications will produce less burning sensation through a mechanism called desensitization. A small clinical trial examined the effects of capsaicin taffy as a treatment for pain in mucositis, based on the desensitization principle, with the added benefit of the sucrose in the taffy mitigating the initial burn of the capsaicin.[20] The researchers found a significant reduction in pain in 11 American patients who were instructed to allow the candy to dissolve in their mouth for 10 minutes. The pain was found to resolve 10 minutes after the taffy had dissolved. Variable dosages were most helpful for continued pain relief, suggesting that additional research would be needed to find the best universal treatment dosage.

Plantago lanceolata (ribwort) and *Plantago major* (broadleaf plantain) leaf have a long history of use in Western Europe for a wide variety of skin conditions, as well as lesions of the mucosa. They are somewhat mucilaginous in quality and promote rapid healing of the skin and mucosal lesions. A randomized, triple-blind clinical trial compared broadleaf plantain extract to chlorhexidine 0.12% or sodium bicarbonate 5% in 50 Spanish patients with OM due to chemotherapy.[21] There was no difference in efficacy between the treatments in terms of healing time, pain intensity, ability to eat and drink, and overall QoL. Further research is needed, but this simple and safe treatment appears promising.

Glycyrrhiza glabra (licorice) is a demulcent plant with a strong history and modern use for helping patients with peptic and esophageal ulcers. A double-blind clinical trial randomized 60 Iranian patients with radiation-related mucositis to medicated mucoadhesive licorice films or triamcinolone.[22] The two treatments were equally effective in the management of mucositis, with a trend favoring licorice for reducing oral discomfort. Licorice tea was significantly more effective than placebo for radiation mucositis in another double-blind trial in 37 Iranian patients with head and neck cancers.[23] An apparently open trial randomized 75 Indian patients with mucositis due to chemo- and radiotherapy to licorice powder in honey and licorice powder in ghee 10 mL b.i.d., licorice powder in honey only, honey only, and conventional therapy only for seven weeks maximum.[24] Both licorice preparations were more effective than conventional therapy; honey was not. It appears that regardless of dose delivery method, licorice is effective for mucositis.

Plants in the Lamiaceae (mint) family often seem to be helpful for patients with mucositis. A clinical trial examined the effectiveness of *Salvia officinalis* (sage) tea, *Thymus vulgaris* (thyme), and *Mentha* x *piperita* (peppermint) hydrosols administered as a 15 mL oral rinse q.i.d. for 30 seconds for 14 days starting on the first day of chemotherapy, with measurements of OM lesions taken on days 5 and 14, showing significant reductions in the incidence of mucositis compared to the control group.[25] One other double-blind clinical trial investigated the efficacy of peppermint oil and chamomile dried plant in ethanol as a mouthwash in patients receiving chemotherapy and stem-cell transplants.[26] The mouthwash was administered t.i.d., beginning on day 1 of chemotherapy and one week before transplant. The mouthwash significantly reduced the severity of OM in the treatment group, as well as reduced the need for rescue medicines.

Honey has a long history of medicinal use throughout the world. Honey is vulnerary, inflammation modulating, and antimicrobial. Many clinical trials and reviews demonstrate the efficacy of oral honey as a treatment for OM severity, progression, recovery rate, prevention, and QoL.[27–29] Most of the study designs included honey dilutions as a gargle taken t.i.d. A large clinical trial was conducted that demonstrated no significant improvement in symptoms using manuka honey, though this trial had notable compliance and dropout issues and is the only study that used irradiated honey.[30] Positive clinical research has shown thyme-infused honey to be effective in OM treatment for radiotherapy, although the study does not clearly support thyme-infused honey to be more effective than plain honey.[31] Another study compared coffee-infused honey to plain honey and steroids, showing significant improvement in OM symptoms in the coffee-honey group compared to the other two treatment groups.[32] Another clinical trial compared honey to a mixture of honey, olive oil propolis extract, and beeswax (HOPE) to benzocaine (control) and found the most significant improvement overall in the honey group, with the HOPE group also demonstrating effectiveness compared to the control group.[33] This study suggests that olive oil, propolis, and beeswax are also helpful in oral mucositis when combined with honey.

Rhodiola algida (Tibetan rose root) has also been studied as a treatment for mucositis. In an open clinical trial, 130 Chinese women with breast cancer undergoing treatment with 5-FU, epirubicin, and cyclophosphamide were randomized to either Tibetan rose root extract or no additional therapy for 14 days after each chemotherapy cycle.[34] All participants received chlorhexidine 0.2% mouthwash. Oral ulcers were fewer and less severe in the Tibetan rose root treatment group compared to controls.

Treatments for Neuropathy and Myopathy

Many chemotherapy agents used in cancer treatment cause severe peripheral neuropathy, referred to as chemotherapy-induced peripheral neuropathy (CIPN). This side effect is common and can be very limiting to long-term QoL, affecting up to 48% of cancer patients and with up to 40% of these individuals continuing to experience symptoms after treatment is complete.[35,36] Current CIPN treatments have not been shown to be highly effective, and prevention often consists of a pulsed regimen, lower doses, or the discontinuation of the chemotherapeutic agent. Other neuroprotective agents have shown little therapeutic value, including calcium, magnesium, carbamazepine, venlafaxine, glutathione, and N-acetylcysteine.

The Chinese formula Niú Chē Shèn Qì Wán (Life Preserving Kidney Qi Pill, goshajinkigan in Japanese) originated in the text *Jì Shēng Fāng* (Formulas to Aid the Living), written by Yán Yòng-Hé in 1253 CE. Translating from its traditional uses, it has come to be used in modern times for symptoms of peripheral neuropathy such as numbness, cold sensations, and limb pain. The contents of this formula are listed in Table 3.

Several clinical trials have been done on this formula based on preclinical work showing efficacy.[37] In the largest, positive, double-blind clinical trial, 89 Japanese adults with colorectal cancer undergoing chemotherapy, including oxaliplatin (a major cause of CIPN), 5-fluorouracil (5-FU), and leucovorin, were randomized to either take goshajikingan (formulated as granulation) 2.5 g t.i.d. or placebo for 26 weeks.[38] Overall incidence, severity, and time to develop CIPN were all significantly better in the goshajinkigan group compared to controls, with no significant difference in adverse effects between them. There was no evidence that the herbal formula interfered with the efficacy of the chemotherapy. A smaller open clinical trial compared the use of goshajinkigan 2.5 g t.i.d. to vitamin B12 1500 μg q.d. in the treatment of CIPN in 57 Japanese women receiving docetaxel therapy for breast cancer.[39] CIPN was significantly less frequent and less severe in the goshajinkigan group compared to the vitamin B12 group. Adverse effects were mild and not different between these treatment groups.

Another double-blind trial was conducted in Japanese patients with colorectal cancer undergoing treatment with oxaliplatin, 5-FU, and leucovorin.[40] The study intended to enroll 310 participants, but an interim analysis was conducted involving 142 subjects randomized to goshajinkigan 2.5 g t.i.d. or placebo for 24 weeks, sourced from the same company as the prior clinical trial on this formula in colorectal cancer patients cited above. In this trial, the goshajinkigan group was significantly more likely to develop severe (grade 2 or higher) CIPN than the placebo group. Therefore, the trial was halted, and the treatment declared inactive. How this could have such wildly different results from the prior clinical trial is difficult to understand. At this point, the role of goshajinkigan in therapy is unknown, and probably only another clinical trial could clarify the situation.

Gui long tong luo fang is a modern Chinese medicinal formula, apparently developed to treat neuropathies, including CIPN. The formula contains *Astragalus membranaceus* (astragalus, huáng qí) 30 g, *Spatholobus suberectus* (spatholobus, jī xuè téng) root and vine 30 g, *Paeonia lactiflora* (white peony, bái sháo) root without bark 30 g, *Pheretima* spp. (earthworm, dì lóng) 12 g, *Angelica sinensis* (dong quai, dāng guī) prepared root 12 g, *Ligusticum striatum* (Sichuan lovage, chuān xiōng) root 12 g, *Carthamnus tinctorius* (safflower, hóng huā) flower 10 g, *Cinnamomum cassia* (cassia cinnamon, guì zhī) twig 9 g, *Curcuma longa* (turmeric, jiāng huáng) rhizome 9 g, and *Glycyrrhiza uralensis* (Asian licorice, gān cǎo) root 6 g. This amount of herbs is decocted in 200 mL of water until it is cooked down to half that volume twice. Then, the final total liquid is mixed and split into two daily doses. One trial randomized 120 Chinese patients with colorectal cancer receiving oxaliplatin, 5-FU, and leucovorin to either the herbal formula or a placebo, taken starting three days before chemotherapy and lasting for 10 days per chemotherapy cycle.[41] Significantly fewer patients taking gui long tong luo fang developed neuropathy than the placebo group, and onset of neuropathy occurred significantly later in the herb group compared to controls. This meant that the median cumulative dose of oxaliplatin that could be administered was twice as high in the group taking the herbal formula compared to those taking placebo.

Several other traditional Chinese medicine herbal formulas have shown promising results in clinical trials in the treatment or prevention of CIPN. A review article looking at a diversity of preclinical and clinical trials both in Chinese and English compared many herbal formulas and single herbs' therapeutic value for CIPN.[42] Three herbal combinations were of particular interest, as they showed efficacy in single clinical trials: Bǔ yáng huán wǔ tāng (Tonify the Yang to Restore Five-Tenths Decoction), a combination of this formula and liù wèi dì huáng (Six Ingredients with Rehmannia), and a modified

Table 3. Niú Chē Shèn Qì Wán (Life Preserving Kidney Qi Pill, goshajinkigan) Formula

Latin name	Common names	Part used	Amount in formula
Rehmannia glutinosa	Rehmannia, shú dì huáng	Prepared root	10%
Dioscorea japonica	Chinese yam, shān yào	Rhizome	9%
Cornus officinalis	Cornelian cherry, shān zhū yú	Fruit	9%
Wolfiporia cocos	Hoelen, fú líng	Sclerotium	9%
Alisma plantago-aquatica	Water plantain, zé xiè	Rhizome	9%
Paeonia suffruticosa	Mountain peony, mǔ dān pí	Root bark	9%
Achyranthes bidentata	Achyranthes, huái niú xī	Root	14%
Plantago asiatica	Chinese plantain, chē qián zǐ	Seed	9%
Cinnamomum cassia	Cassia cinnamon, ròu guì	Bark	6%
Aconitum carmichaelii	Sichuan aconite, fù zǐ	Prepared lateral root	8%

version of chái hú lóng gǔ mǔ lì wán (Bupleurum, Dragon Bone, and Oyster Shell Teapills). Clearly, more research is needed, but these traditional Chinese formulas look promising.

A review paper looked at 24 quality clinical trials conducted in mainland China (and all published only in Chinese), examining the efficacy of astragalus root as a single herb or in formulas both topically and internally for the treatment of CIPN.[43] The trials consistently demonstrated effectiveness with astragalus root alone, in formula, and both topically and orally in improving symptoms of CIPN. Combined with its immune-modulating effects discussed in part 1 of this paper, astragalus can be very helpful for patients undergoing cancer chemotherapy. A typical dose would be at least 5 g t.i.d. as crude herb, powder, or granulation, or of glycerite or tincture 5–10 mL t.i.d.

Sháo yào gān cǎo tāng (Peony and Licorice Decoction, shakuyaku-kanzo-tō in Japanese) is an ancient Chinese formula. It originated in one of the most famous Chinese medicine books, the *Shāng Hán Lùn* (Treatise on Cold Damage Disorders) by Zhāng Zhòng-Jǐng, published in 220 CE. The formula contains equal amounts of Asian licorice and white peony roots. It is much esteemed for treating muscle cramps from a wide variety of causes. One retrospective case series found giving 7.5 g of granulation of the formula daily to 21 Japanese women with ovarian cancer undergoing chemotherapy with paclitaxel and carboplatin effective at significantly reducing pain in 43% of them.[44] A prospective open trial randomized 50 Japanese adults with non–small cell lung cancer undergoing paclitaxel and carboplatin chemotherapy to the same dose (2.5 g t.i.d.) of granulation of shakuyaku-kanzo-tō for 21 days during treatment or no additional therapy.[45] Duration and severity of myalgia and arthralgia were significantly less in the herbal group compared to controls. Additionally, significantly fewer rescue medications (mostly nonsteroidal anti-inflammatory drugs) were needed in the treatment group compared to controls (one control patient developed a duodenal ulcer due to these medications). This formula contains sufficient licorice potentially to cause hypokalemia and hypertension.[46,47] Patients taking it should have their blood pressure monitored weekly and should eat a high potassium diet to help prevent that from happening.

Silymarin as an Organ Protector

Hand-foot syndrome, also called palmar-plantar erythrodysesthesia, is a painful side effect of some chemotherapy agents consisting of redness, swelling, and pain, with occasionally blisters, on the palms of the hands and/or the soles of the feet, and rarely on other skin surfaces. This side effect can severely impact QoL. Silymarin, a complex of flavonolignans extracted from the seeds of *Silybum marianum* (milk thistle; Fig. 1), has been studied for preventing hand-food syndrome due to capecitabine in one trial. Forty people receiving capecitabine treatment for gastrointestinal cancer were randomized to apply placebo or silymarin gel 1% b.i.d. to their palms and soles.[48] Treatment was started the first day of chemotherapy and continued for nine weeks. Both groups showed an increase in hand-food syndrome symptoms during chemotherapy, but the treatment group showed a significant delay in development and progression of these symptoms compared to controls.

Silymarin did not fare as well in offsetting the nephrotoxicity of cisplatin. An initial open trial randomized 60 patients with a range of cancers (all being treated with cisplatin) to take silymarin 140 mg b.i.d., beginning seven days before chemotherapy, or no additional treatment for at least two weeks.[49] Serum creatinine was significantly lower in the silymarin group compared to controls at the end of the study. A smaller double-blind trial randomized 24 patients with a range of cancers undergoing cisplatin chemotherapy to silymarin 140 mg t.i.d. or placebo.[50] Adjunctive treatment was started one or two days before chemotherapy in all cases and continued throughout three 21-day cycles of cisplatin. All patients were given intravenous hydration with magnesium and potassium before and after cisplatin infusions; this is standard therapy to reduce nephrotoxicity. No outcome measure, including incidence of acute kidney injury and glomerular filtration rate, showed any difference between the treatment groups. There were no adverse effects due to silymarin. At present, it does not appear that this dosing schedule of silymarin is effective for cisplatin nephrotoxicity.

A potential problem with the nephrotoxicity study was the use of an overly refined extract of silymarin only. One double-blind trial randomized 49 children with acute lymphocytic leukemia (ALL) and elevated serum transferases due to chemotherapy to either whole milk thistle 240 mg (standardized to contain 97 mg silibinin) or placebo.[51] Capsules were dosed to deliver 5.1 mg silibinin/kg body weight. After 56 days of treatment during chemotherapy, serum aspartate transaminase (AST) levels were significantly lower in the milk thistle group compared to the placebo group. Significantly more patients taking milk thistle had at least a 50% reduction in serum bilirubin levels compared to placebo patients. There was no difference in adverse effects (digestive upset) between the two groups, though adherence to treatment was significantly lower in the milk thistle group.

A different double-blind trial randomized 80 children with ALL about to undergo methotrexate chemotherapy to take 140 mg silymarin (in capsules or syrup) t.i.d. or placebo.[52] Though alanine aminotransferase, AST, and alkaline phosphatase levels rose in both groups, all three were significantly lower in the silymarin group compared to the placebo group after one week of methotrexate-based chemotherapy. Additionally, prothrombin time, prothrombin activity, serum creatinine, serum cystatin C, and urine N-acetyl-beta-D-glucosaminidase (a marker of renal damage) were all significantly lower in the silymarin group compared to the placebo group. As in the prior trial, there was no evidence of interference with the chemotherapy in either group.

The preclinical literature on other natural products as organ-protective adjuncts to cisplatin chemotherapy is extremely extensive. A sampling of these studies is listed in Table 4. It is

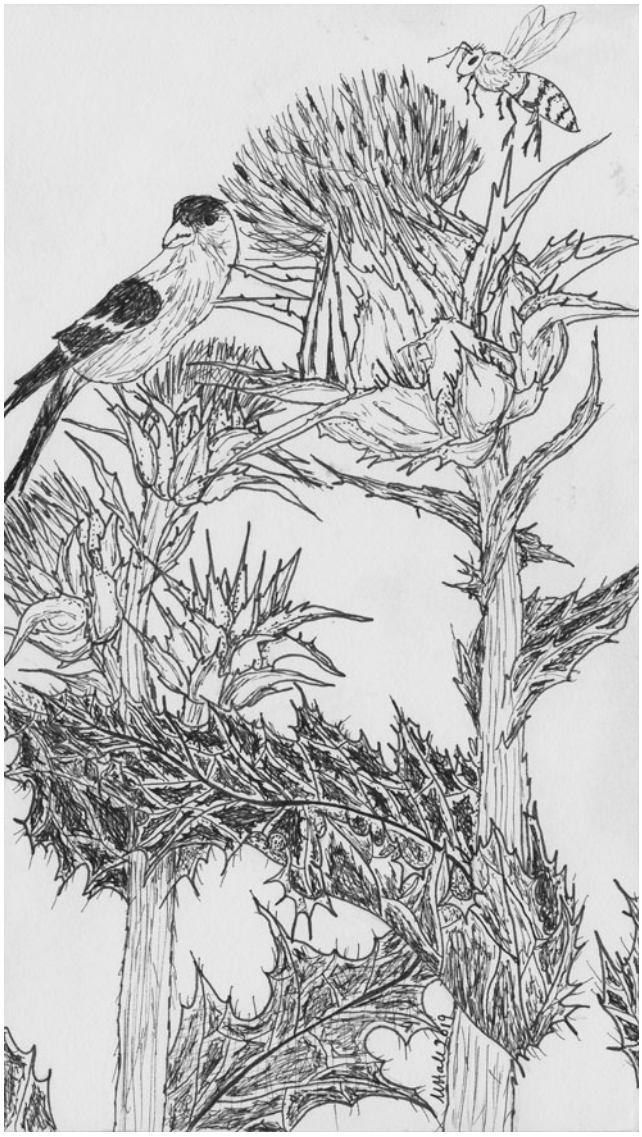

Figure 1. ***Silybum marianum*. Drawing by Meredith Hale and reprinted with permission.**

important to note that in none of these studies was there evidence that the herbs worked by simply blocking the effects of cisplatin, thus eliminating the benefits of the drug along with its toxicities.

Cardioprotection

A number of chemotherapy agents are notable for causing irreversible damage to the heart. Anthracyclines such as daunorubicin, doxorubicin, epirubicin, and idarubicin; alkylating agents such as busulfan, carboplatin, carmustine, chlormethine, cisplatin, cyclophosphamide, and mitomycin; taxanes such as docetaxel, cabazitaxel, and paclitaxel; topoisomerase inhibitors such as etoposide, tretinoin, and vinca alkaloids; and antimetabolites such as cladribine, cytarabine, and 5-FU are the main causes of cardiac toxicity. Anthracyclines are the major offenders. Some biologic drugs, notably trastuzumab, bevacizumab, lapatinib, and sunitinib, cause reversible cardiac damage. Though a large number of herbs and herbal constituents have been shown to protect against the toxicity of these drugs in preclinical research, there is a surprising dearth of clinical trials in this area.[53]

A double-blind, placebo-controlled, randomized clinical trial demonstrated effectiveness of salidroside, a glycoside isolated in *Rhodiola rosea* (rose root, arctic root), in protecting against early left ventricular systolic dysfunction caused by chemotherapy.[54] In this trial, 60 Chinese patients being treated for breast cancer with epirubicin were split into placebo and treatment groups. Salidroside was given at doses of 600 mg q. d., beginning one week prior to the start of chemotherapy, and continued for the entire treatment regimen. Compared to placebo, this treatment significantly improved markers of cardiac health as epirubicin doses accumulated. A similar trial in 42 Chinese patients undergoing epirubicin therapy randomized them to either rose root extract or no additional therapy for one month.[55] Several measures of cardiac function were significantly better in the rose root treatment group compared to controls.

Miscellaneous Additional Adjuncts

Doxorubicin is also known to cause insulin resistance and hyperglycemia. *Allium cepa* (onion) has been studied to counteract this problem. In the first double-blind trial, 46 Iranian women undergoing doxorubicin-containing chemotherapy were randomized to eat 100–160 g of onion per day, or 30–40 g per day in the control group.[56] Treatment was started two days after the second course of chemotherapy. After eight weeks, serum transaminase levels were significantly lower in the high-onion group compared to the low-onion group. Alkaline phosphatase levels were nonsignificantly lower in the high-onion group compared to the low-onion group. Surprisingly, two tumor marker levels (carcinoembryonic antigen and CA-125) were significantly reduced in the high-onion group compared to the low-onion group, suggesting onion could enhance the efficacy of chemotherapy. Fasting serum glucose and insulin levels were significantly reduced, while insulin sensitivity (measured several different ways) was significantly improved by the high-onion versus low-onion diet.[57]

Annona muricata (soursop), a tropical tree belonging to the Annonaceae family, has historical use in the treatment of parasites, infections, and tumors, as well as for improving nutritional status through improving absorption of nutrients.[58] A small double-blind, randomized, placebo-controlled trial demonstrated that an ethanol extract of *A. muricata* leaf given to colorectal cancer patients improved nutritional status and blood values of antitumor constituents with no effect on hemoglobin or other blood values.[59] Nutritional status and absorption of nutrients is a big concern in cancer patients and

Table 4. Preclinical Research on Natural Products as Organ Protectors Against Cisplatin

Herb/compound	Effect	Model	Reference
Panax quinquefolius (American ginseng)	Fruit: Nephroprotective Leaf: Nephroprotective	Mice	Ma 2017[a,b]
Panax ginseng (Asian ginseng)	Fruit, root, and ginsenoside Rg5: Nephroprotective Root: Otoprotective	Mice Rats	Qi 2017[c]; Park 2015[d]; Li 2016[e]; Olgun 2016[f]; Kim 2015[g]
Panax notoginseng (sanqi ginseng, sān qī) saponins	Nephroprotective	Rats	Liu 2014[h]
Schisandra chinensis (schisandra, wǔ wèi zǐ) and schisandrin B	Nephroprotective	Rats	Li 2018[i]; Huang 2017[j]; Li 2012[k]
Schisandra sphenanthera (southern schisandra, nán wǔ wèi zǐ)	Nephroprotective	Mice	Jin 2015[l]
Nigella sativa (black cumin)	Nephroprotective	Rats	Farooqui 2017[m,n]; Cascella 2017[o]
Acacia hydaspica (Indian cockspur thorn)	Lung and hepatoprotective	Rats	Afsar 2018[p]; Afsar 2017[q]
Andrographis paniculata (andrographis, chuān xīn lián)	Nephroprotective; increases anticancer effects of cisplatin in vitro	Rats	Adeoye 2018[r]; Li 2017[s]
Trigonella foenum-graecum (fenugreek)	Hepato-, nephro-, and testiculoprotective	Rats	Hegazy 2015[t]; Hamza 2016[u]
Terminalia arjuna (arjun), arjunolic acid	Nephroprotective	Rats	Sherif 2015[v]; Elsherbiny 2016[w]
Punica granatum (pomegranate)	Nephroprotective	Rats	Boroushaki 2015[x]; Bakõr 2015[y]
Curcuma longa (turmeric), tetrahydrocurcumin, curcumin	Nephroprotective, potentiates anticancer effects of cisplatin (crude extract superior to curcumin alone)	Rats	Rezaee 2017[z]; Kukula-Koch 2017[aa]

[a]Ma ZN, Liu Z, Wang Z, et al. Supplementation of American ginseng berry extract mitigated cisplatin-evoked nephrotoxicity by suppressing ROS-mediated activation of MAPK and NF-κB signaling pathways. Food Chem Toxicol 2017;110:62–73.
[b]Ma ZN, Li YZ, Li W, et al. Nephroprotective effects of saponins from leaves of *Panax quinquefolius* against cisplatin-induced acute kidney injury. Int J Mol Sci 2017;18:E1407.
[c]Qi ZL, Wang Z1, Li W, et al. Nephroprotective effects of anthocyanin from the fruits of *Panax ginseng* (GFA) on cisplatin-induced acute kidney injury in mice. Phytother Res 2017;31:1400–1409.
[d]Park JY, Choi P, Kim T, et al. Protective effects of processed ginseng and its active ginsenosides on cisplatin-induced nephrotoxicity: in vitro and in vivo studies. J Agric Food Chem 2015;63:5964–5969.
[e]Li W, Yan MH, Liu Y, et al. Ginsenoside Rg5 ameliorates cisplatin-induced nephrotoxicity in mice through inhibition of inflammation, oxidative stress, and apoptosis. Nutrients 2016;8:E566.
[f]Olgun Y, Kõrkõm G, Altun Z, et al. Protective effect of Korean red ginseng on cisplatin ototoxicity: Is it effective enough? J Int Adv Otol 2016;12:177–183.
[g]Kim SJ, Kwak HJ, Kim DS, et al. Protective mechanism of Korean red ginseng in cisplatin-induced ototoxicity through attenuation of nuclear factor-κB and caspase-1 activation. Mol Med Rep 2015;12:315–322.
[h]Liu X, Huang Z, Zou X, et al. *Panax notoginseng* saponins attenuates cisplatin-induced nephrotoxicity via inhibiting the mitochondrial pathway of apoptosis. Int J Clin Exp Pathol 2014;7:8391–8400.
[i]Li YZ, Ren S, Yan XT, et al. Improvement of cisplatin-induced renal dysfunction by *Schisandra chinensis* stems via anti-inflammation and anti-apoptosis effects. J Ethnopharmacol 2018;217:228–237.
[j]Huang H, Shen Z, Geng Q, et al. Protective effect of *Schisandra chinensis* bee pollen extract on liver and kidney injury induced by cisplatin in rats. Biomed Pharmacother 2017;95:1765–1776.
[k]Li M, Jin J, Li J, et al. Schisandrin B protects against nephrotoxicity induced by cisplatin in HK-2 cells via Nrf2-ARE activation. Yao Xue Xue Bao 2012;47:1434–1439 [in Chinese].
[l]Jin J, Li M, Zhao Z, et al. Protective effect of wuzhi tablet (*Schisandra sphenanthera* extract) against cisplatin-induced nephrotoxicity via Nrf2-mediated defense response. Phytomedicine 2015;22:528–535.
[m]Farooqui Z, Shahid F, Khan AA, Khan F. Oral administration of *Nigella sativa* oil and thymoquinone attenuates long term cisplatin treatment induced toxicity and oxidative damage in rat kidney. Biomed Pharmacother 2017;96:912–923.
[n]Farooqui Z, Ahmed F, Rizwan S, et al. Protective effect of *Nigella sativa* oil on cisplatin induced nephrotoxicity and oxidative damage in rat kidney. Biomed Pharmacother 2017;85:7–15.
[o]Cascella M, Palma G, Barbieri A, et al. Role of *Nigella sativa* and its constituent thymoquinone on chemotherapy-induced nephrotoxicity: Evidences from experimental animal studies. Nutrients 2017;9:E625.
[p]Afsar T, Razak S, Almajwal A, Khan MR. *Acacia hydaspica* R Parker ameliorates cisplatin induced oxidative stress, DNA damage and morphological alterations in rat pulmonary tissue. BMC Complement Altern Med 2018;18:49.
[q]Afsar T, Razak S, Almajwal A, Rashid Khan M. Modulatory influence of *Acacia hydaspica* R Parker ethyl acetate extract against cisplatin inveigled hepatic injury and dyslipidemia in rats. BMC Complement Altern Med 2017;17:307.
[r]Adeoye BO, Asenuga ER, Oyagbemi AA, et al. The protective effect of the ethanol leaf extract of *Andrographis paniculata* on cisplatin-induced acute kidney injury in rats through nrf2/KIM-1 signalling pathway. Drug Res (Stuttg) 2018;68:23–32.
[s]Li L, Yue GG, Lee JK, et al. The adjuvant value of *Andrographis paniculata* in metastatic esophageal cancer treatment—from preclinical perspectives. Sci Rep 2017;7:854.
[t]Hegazy MG, Emam MA. Ethanolic extract of *Trigonella foenum graecum* attenuates cisplatin-induced nephro- and hepatotoxicities in rats. Cell Mol Biol (Noisy-le-grand) 2015;61:81–87.
[u]Hamza AA, Elwy HM, Badawi AM. Fenugreek seed extract attenuates cisplatin-induced testicular damage in Wistar rats. Andrologia 2016;48:211–221.
[v]Sherif IO. Amelioration of cisplatin-induced nephrotoxicity in rats by triterpenoid saponin of *Terminalia arjuna*. Clin Exp Nephrol 2015;19:591–597.
[w]Elsherbiny NM, Eladl MA, Al-Gayyar MM. Renal protective effects of arjunolic acid in a cisplatin-induced nephrotoxicity model. Cytokine 2016;77:26–34.
[x]Boroushaki MT, Rajabian A, Farzadnia M, et al. Protective effect of pomegranate seed oil against cisplatin-induced nephrotoxicity in rat. Ren Fail 2015;37:1338–1343.
[y]Bakõr S, Yazgan ÜC, İbiloğlu İ, et al. The protective effect of pomegranate extract against cisplatin toxicity in rat liver and kidney tissue. Arch Physiol Biochem 2015;121:152–156.
[z]Rezaee R, Momtazi AA, Monemi A, Sahebkar A. Curcumin: A potentially powerful tool to reverse cisplatin-induced toxicity. Pharmacol Res 2017;117:218–227.
[aa]Kukula-Koch W, Grabarska A, èuszczki J, et al. Superior anticancer activity is demonstrated by total extract of *Curcuma longa* L. as opposed to individual curcuminoids separated by centrifugal partition chromatography. Phytother Res 2018;32:933–942.

cancer treatment, suggesting soursop may be a valuable botanical intervention. In addition, the study, though small, supports preclinical trials in demonstrating that the antitumor constituents of soursop extract are absorbed into the bloodstream, indicating that they can then circulate to other areas of the body. Ethanol soluble fraction of soursop leaf water extract was given in a capsule form at a dose of 300 mg after breakfast for eight weeks in this trial.

A small randomized, double-blind, placebo-controlled trial was conducted on a herbal blend called MB-6, demonstrating an increase in the effectiveness of chemotherapy in colon cancer patients when MB-6 is administered concurrently.[60] MB-6 is a combination of soybean extract, green tea extract, *Taiwanofungus camphoratus* (stout camphor fungus), formerly *Antrodia camphorata* mycelium, spirulina, grape seed extract, and curcumin. In this study of 72 Chinese participants, the treatment group showed a significantly lower disease progression rate than the placebo control group, although no significant difference was found in the overall survival rate. The patients were undergoing FOLFOX chemotherapy regimen for colon cancer in combination with either MB-6 or placebo for 16 weeks. The findings of this clinical trial support the preliminary preclinical trial results, and suggest a valuable adjunctive therapy to aid in the effectiveness of chemotherapy in patients with metastatic colon cancer, with no adverse side effects from this botanical treatment.

Conclusion

Herbal medicines offer a wide range of potential benefits to patients undergoing chemotherapy. Many substances have been reviewed that can help ease nausea and vomiting, mucositis, neuropathy, and a range of other problems. Some of the agents discussed here have been assessed in multiple clinical trials, but all of them could benefit from larger, better designed trials. Even so, the high degree of safety and low cost of most of the treatments or preventative measures suggested here can still lead to their clinical use, even without definitive proof of efficacy. ■

References

1. Herrstedt J, Dombernowsky P. Anti-emetic therapy in cancer chemotherapy: Current status. Basic Clin Pharmacol Toxicol 2007;101:143–150.

2. Di Maio M, Baratelli C, Bironzo P, et al. Efficacy of neurokinin-1 receptor antagonists in the prevention of chemotherapy-induced nausea and vomiting in patients receiving carboplatin-based chemotherapy: A systematic review and meta-analysis. Crit Rev Oncol Hematol 2018;124:21–28.

3. dos Santos LV, Souza FH, Brunetto AT, et al. Neurokinin-1 receptor antagonists for chemotherapy-induced nausea and vomiting: A systematic review. J Natl Cancer Inst 2012;104:1280–1292.

4. Ryan JL, Heckler CE, Roscoe JA, et al. Ginger (*Zingiber officinale*) reduces acute chemotherapy-induced nausea: A URCC CCOP study of 576 patients. Support Care Cancer 2012;20:1479–1489.

5. Pillai AK, Sharma KK, Gupta YK, Bakhshi S. Anti-emetic effect of ginger powder versus placebo as an add-on therapy in children and young adults receiving high emetogenic chemotherapy. Pediatr Blood Cancer 2011;56:234–238.

6. Chang WP, Peng YX. Does the oral administration of ginger reduce chemotherapy-induced nausea and vomiting?: A meta-analysis of 10 randomized controlled trials. Cancer Nurs 2018 Oct 6 [ePub ahead of print]; DOI: 10.1097/NCC.0000000000000648.

7. Nakamura M, Nakamori M, Ojima T, et al. The effects of rikkunshito on body weight loss after esophagectomy. J Surg Res 2016;204:130–138.

8. Ohnishi S, Watari H, Kanno M, et al. Additive effect of rikkunshito, an herbal medicine, on chemotherapy-induced nausea, vomiting, and anorexia in uterine cervical or corpus cancer patients treated with cisplatin and paclitaxel: Results of a randomized Phase II study (JORTC KMP-02). J Gynecol Oncol 2017;28:1–10.

9. Takiguchi S, Hiura Y, Takahashi T, et al. Effect of rikkunshito, a Japanese herbal medicine, on gastrointestinal symptoms and ghrelin levels in gastric cancer patients after gastrectomy. Gastric Cancer 2013;16:176–174.

10. Gunji S, Ueda S, Yoshida M, et al. Effects of rikkunshito, a kampo medicine, on quality of life after proximal gastrectomy. J Surgical Res 2013;185:575–580.

11. Darmani NA. Mechanisms of broad-spectrum antiemetic efficacy of cannabinoids against chemotherapy-induced acute and delayed vomiting. Pharmaceuticals 2010;3:2930–2955.

12. Smith LA, Azariah F, Lavender VT, et al. Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy. Cochrane Database Syst Rev 2015;(11):CD009464.

13. Machado Rocha FC, Stéfano SC, De Cássia Haiek R, et al. Therapeutic use of *Cannabis sativa* on chemotherapy-induced nausea and vomiting among cancer patients: Systematic review and meta-analysis. Eur J Cancer Care (Engl) 2008;17:431–443.

14. Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for medical use: A systematic review and meta-analysis. JAMA 2015;313:2456–2473.

15. Parker LA, Rock EM, Limebeer CL. Regulation of nausea and vomiting by cannabinoids. Br J Pharmacol 2011;163:1411–1422.

16. Chang AE, Shiling DJ, Stillman RC, et al. Delata-9-tetrahydrocannabinol as an antiemetic in cancer patients receiving high-dose methotrexate. A prospective, randomized evaluation. Ann Intern Med 1979;91:819–824.

17. Chen MH, May BH, Zhou IW, et al. Integrative medicine for relief of nausea and vomiting in the treatment of colorectal cancer using oxaliplatin-based chemotherapy: A systematic review and meta-analysis. Phytother Res 2016;30:741–753.

18. Mirandzadeh S, Adib-Hajbaghery M, Soleymanpoor L, Ehsani M. Effect of adding the herb *Achillea millefolium* on mouthwash on chemotherapy induced oral mucositis in cancer patients: A double-blind randomized controlled trial. Eur J Oncol Nursing 2015;19:207–213.

19. Gomes VTS, Gomes RNS, Gomes MS, et al. Effects of *Matricaria recutita* (L) in the treatment of oral mucositis. ScientificWorldJournal 2018;2018:4392184.

20. Berger A, Henderson M, Nadoolman W, et al. Oral capsaicin provides temporary relief for oral mucositis pain secondary to chemotherapy/radiation therapy. J Pain Symptom Manage 1995;10:243–248.

21. Cabrera-Jaime S, Martínez C, Ferro-Garcia T, et al. Efficacy of *Plantago major*, chlorhexidine 0.12% and sodium bicarbonate solution in the treatment of oral mucositis in cancer patients with solid tumour: A feasibility randomized triple-blind Phase III clinical trial. Eur J Oncol Nursing 2018;32:40–47.

22. Ghalayani P, Ememi H, Pakravan F, Nasr Isfahani M. Comparison of triamcinolone acetonide mucoadesive film with licorice mucoadhesive film

on radiotherapy-induced oral mucositis: A randomized double-blinded clinical trial. Asia Pac J Clin Oncol 2017;13:48–56.

23. Najafi S, Koujan SE, Manifar S, et al. Preventive effect of *Glycyrrhiza glabra* extract on oral mucositis in patients under head and neck radiotherapy: A randomized clinical trial. J Dent (Tehran) 2017;14:267–274.

24. Das D, Agarwal SK, Chandola HM. Protective effect of yashtimadhu (*Glycyrrhiza glabra*) against side effects of radiation/chemotherapy in head and neck malignancies. Ayu 2011;32:196–199.

25. Mutluay Yayla E, Izgu N, Ozdemir L, et al. Sage tea-thyme-peppermint hydrosol oral rinse reduces chemotherapy-induced oral mucositis: A randomized controlled pilot study. Complement Ther Med 2016;27: 58–64.

26. Tavakoli Ardakani M, Ghassemi S, Mehdizadeh M, et al. Evaluating the effect of *Matricaria recutita* and *Mentha piperita* herbal mouthwash on management of oral mucositis in patients undergoing hematopoietic stem cell transplantation: A randomized, double blind, placebo controlled clinical trial. Complement Ther Med 2016;29:29–34.

27. Kobya Bulut D, Güdücü Tüfekci F. Honey prevents oral mucositis in children undergoing chemotherapy: A quasi-experimental study with a control group. Complement Ther Med 2016;29:132–140.

28. Khanal B, Baliga M, Uppal N. Effect of topical honey on limitation of radiation-induced oral mucositis: An intervention study. Int J Oral Maxillofac Surg 2010;39:1181–1185.

29. Xu JL, Xia R, Sun ZH, et al. Effects of honey use on the management of radio/chemotherapy-induced mucositis: A meta-analysis of randomized controlled trials. Int J Oral Maxillofac Surg 2016;45:1618–1625.

30. Hawley P, Hovan A, McGahan CE. A randomized placebo-controlled trial of manuka honey for radiation-induced oral mucositis. Support Cancer Care 2014;22:751–761.

31. Charalambous M, Raftopoulos V, Paikousis L, et al. The effect of the use of thyme honey in minimizing radiation-induced oral mucositis in head and neck cancer patients: A randomized controlled trial. Eur J Oncol Nursing 2018;34:89–97.

32. Raeessi MA, Raeessi N, Panahi Y, et al. "Coffee plus honey" versus "topical steroid" in the treatment of chemotherapy-induced oral mucositis: A randomized controlled trial. BMC Complement Altern Med 2014; 14:293.

33. Abdulrhman M, Samir El Barbary N, et al. Honey and a mixture of honey, beeswax, and olive oil-propolis extract in treatment of chemotherapy-induced oral mucositis: A randomized controlled pilot study. Pediatr Hematol Oncol 2012;29:285–292.

34. Loo WT, Jin LJ, Chow LW, et al. *Rhodiola algida* improves chemotherapy-induced oral mucositis in breast cancer patients. Expert Opin Investig Drugs 2010;19:S91–100.

35. 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;155:2461–2470.

36. Park SB, Goldstein D, Krishnan AV, et al. Chemotherapy-induced peripheral neurotoxicity: A critical analysis. CA Cancer J Clin 2013;63:419–437.

37. Cascella M, Muzio MR. Potential application of the Kampo medicine goshajinkigan for prevention of chemotherapy-induced peripheral neuropathy. J Integr Med 2017;15:77–87.

38. Kono T, Hata T, Morita S, et al. Goshajinkigan oxaliplatin neurotoxicity evaluation (GONE): A Phase 2, multicenter, randomized, double-blind, placebo-controlled trial of goshajinkigan to prevent oxaliplatin-induced neuropathy. Cancer Chemother Pharmacol 2013;72: 1283–1290.

39. Abe H, Kawai Y, Mori T. The Kampo medicine goshajinkigan prevents neuropathy in breast cancer patients treated with docetaxel. Asian Pac J Cancer Prev 2013;14:6351–6356.

40. Oki E, Emi Y, Kojima H, et al. Preventive effect of *Goshajinkigan* on peripheral neurotoxicity of FOLFOX therapy (GENIUS trial): A placebo-controlled, double-blind, randomized Phase III study. Int J Clin Oncol 2015;20:767–775.

41. Liu Y, Zhu G, Han L, et al. Clinical study on the prevention of oxaliplatin-induced neurotoxicity with guilongtongluofang: Results of a randomized, double-blind, placebo-controlled trial. Evid Based Complement Alternat Med 2013;2013:541217.

42. Schröder S, Beckmann K, Franconi G, et al. Can medical herbs stimulate regeneration or neuroprotection and treat neuropathic pain in chemotherapy-induced peripheral neuropathy? Evid Based Complement Alternat Med 2013;2013:423713.

43. Deng B, Jia L, Cheng Z. Radix astragali-based Chinese herbal medicine for oxaliplatin-induced peripheral neuropathy: A systematic review and meta-analysis. Evid Based Complement Alternat Med 2016;2016: 2421876.

44. 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;31:1537–1540 [in Japanese].

45. 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;17:315–320.

46. Homma M, Ishihara M, Qian W, Kohda Y. Effects of long term administration of shakuyaku-kanzo-to and shosaiko-to on serum potassium levels. Yakugaku Zasshi 2006;126:973–978 [in Japanese].

47. Kinoshita H, Okabayashi M, Kaneko M, et al. Shakuyaku-kanzo-to induces pseudoaldosteronism characterized by hypokalemia, rhabdomyolysis, metabolic alkalosis with respiratory compensation, and increased urinary cortisol levels. J Altern Complement Med 2009;15:439–443.

48. Elyasi S, Shojaee FSR, Allahyari A, Karimi G. Topical silymarin administration for prevention of capecitabine-induced hand-foot syndrome: A randomized, double-blinded, placebo-controlled clinical trial. Phytother Res 2017;31:1323–1329.

49. Momeni A, Hajigholami A, Geshnizjani S, Kheiri S. Effect of silymarin in the prevention of cisplatin nephrotoxicity, a clinical trial study. J Clin Diag Res 2015;9:11–13.

50. Shahbazi F, Sadighi S, Dashti-Khavidaki S, et al. Effect of silymarin administration on cisplatin nephrotoxicity: Report from a pilot, randomized, double-blinded, placebo-controlled clinical trial. Phytother Res 2015;29: 1046–1053.

51. Ladas EJ, Kroll DJ, Oberlies NH, et al. A randomized, controlled, double-blind, pilot study of milk thistle for the treatment of hepatotoxicity in childhood acute lymphoblastic leukemia (ALL). Cancer 2010;116:506–513.

52. Hagag AA, Elgamsy MA, El-Asy HM, Mabrouk MM. Protective role of silymarin on hepatic and renal toxicity induced by MTX based chemotherapy in children with acute lymphoblastic leukemia. Mediterr J Hematol Infect Dis 2016;8:e2016043.

53. Abushouk AI, Ismail A, Salem AMA, et al. Cardioprotective mechanisms of phytochemicals against doxorubicin-induced cardiotoxicity. Biomed Pharmacother 2017;90:935–946.

54. Zhang H, Shen WS, Gao CH, et al. Protective effects of salidroside on epirubicin-induced early left ventricular regional systolic dysfunction in patients with breast cancer. Drugs R D 2012;12:101–106.

55. Shen WS, Gao CH, Zhang H. Effect of rhodiola on serum troponin 1, cardiac integral backscatter and left ventricle ejective fraction of patients who received epirubicin-contained chemotherapy. Zhongguo Zhong Xi Yi Jie He Za Zhi. 2010;30:1250–1252 [in Chinese].

56. Jafarpour-Sadegh F, Montazeri V, Adili A, et al. Effects of fresh yellow onion consumption on CEA, CA125 and hepatic enzymes in breast cancer

patients: A double-blind randomized controlled clinical trial. Asian Pac J Cancer Prev. 2015;16:7517–7522.

57. Jafarpour-Sadegh F, Montazeri V, Adili A, et al. Consumption of fresh yellow onion ameliorates hyperglycemia and insulin resistance in breast cancer patients during doxorubicin-based chemotherapy: A randomized controlled clinical trial. Integr Cancer Ther 2017;16:276–289.

58. Quílez AM, Fernández-Arche MA, García-Giménez MD, De la Puerta R. Potential therapeutic applications of the genus *Annona*: Local and traditional uses and pharmacology. J Ethnopharmacol 2018;225:244–270.

59. Indrawati L, Ascobat P, Bela B, et al. The effect of an *Annona muricata* leaf extract on nutritional status and cytotoxicity in colorectal cancer: A randomized controlled trial. Asia Pac J Clin Nutr 2017;26:606–612.

60. Chen WTL, Yang TS, Chen HC, et al. Effectiveness of a novel herbal agent MB-6 as a potential adjunct to 5-fluoracil-based chemotherapy in colorectal cancer. Nutr Res 2014;34:585–594.

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