Current Research and Clinical Applications

Chinese Herbal Medicines for Toxicity Reduction in Cancer Chemotherapy

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Cancer is a leading killer of Australians. Chemotherapy is a major modality for the treatment of cancer, but it often fails due to dose-limiting toxicities and tumour resistance. Cytotoxic therapeutic agents kill not only cancer cells but normal cells, inducing host organ injuries and causing severe blood and gastrointestinal toxicities. For example, administration of irinotecan, 5-fluouracil, oxaliplatin, capecitabine, and raltitrexed are associated with diarrhoea in 50–80% of patients in randomised phase III trials.[1] The incidence of grade 3 or 4 diarrhoea was up to 40% of patients with use of irinotecan.[2] Such toxicities limit the further evaluation of more aggressive regimens and significantly decrease the quality of life of patients. In clinical practice, a number of standard supportive therapies such as growth factors and symptom-alleviating therapies (e.g. analgesics and anti-diarrhoea agents) are available in cancer chemotherapy to protect the bone marrow and gastrointestinal tracts and alleviate organ-toxicity associated symptoms. However, several studies have found that a substantial number of cancer patients also use Chinese herbal medicines (CHM) in combination with anticancer drugs in an attempt to reduce drug toxicities and to consolidate the immune system.[3]

A recent double-blind, placebo-controlled and randomised clinical trial was conducted by Mok et al.[4] to investigate the efficacy of toxicity reduction of CHM in 120 patients with early-stage resected breast or colon cancer. These patients were treated with adjuvant chemotherapy in combination with a herbal formula consisting of multiple CHMs for 14 days or with a placebo. The adjuvant chemotherapy for patients with breast cancer consisted of adriamycin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 given three-weekly for four cycles. All patients received intravenous granisetron 3 mg and dexamethasone 10 mg as prophylactic antiemetic therapy. The patients with colon cancer were treated with 5-fluorouracil 425 mg/m^2 and folinic acid 20 mg/m^2 given once daily on days 1–5 of a 28-day cycle for six cycles. The colon cancer patients did not routinely receive prophylactic antiemetic therapy, but metoclopramide and dexamethasone were given if they experienced nausea or vomiting. According to the patient's condition, the well-trained herbalist prescribed a combination of single-itemised herbs from the stock of commonly used herbs and the patients were randomised to receive either the prescribed herbal combination or placebo for 14 days. Two hundred and twenty-five types of the commonly used herbs were stocked in packaged form (see Box 1). All these herbs are listed in the China Pharmacopoeia.[5] Each package contained 3–10 g of water-soluble herbal granules that were manufactured at a Good Manufacture Practice standard facility. To prepare the herbal granules, each herb was boiled in hot water according to the traditional method of herbal tea preparation. The raw materials for the placebo included Chinese Puer tea (*Camellia sinensis var. assamica*), black bean paste (*Dandouchi*, *Semen Sojae praeparatum*), malt sugar (*Maiya*, *Fructus Hordei vulgaris germinatus*), food colour, and artificial flavour. The primary end points were haematologic and non-haematologic toxic effects according to the National Cancer Institute Common Toxicity Criteria (version 2).[6] Secondary end points included quality of life during therapy, treatment compliance, dose intensity, and tumour recurrence rate.

The incidence of grade 3/4 anaemia, leucopoenia, neutropoenia, and thrombocytopoenia in patients treated with CHM for 14 days is not significantly different from that in patients receiving placebo only (5.4%, 47.3%, 52.7% and 1.8% vs 1.8%, 32.2%, 44.7%, and 3.6%, respectively). However, the incidence of nausea is significantly decreased in the CHM-treated group compared to the control group (14.6% vs 35.7%). There were no significant differences in other non-haematologic toxicities between the CHM and placebo groups. The change in the score for each domain in the European Organisation for Research and Treatment of Cancer (EORTC) QLQC30 between each cycle of chemotherapy and baseline was compared and there was no significant difference between the CHM and placebo groups.

CLINICAL RELEVANCE

The findings from the above study indicate that CHM does not alleviate chemotherapy-induced haematological toxicity, but significantly reduces cytotoxic drug-induced nausea. The results are encouraging and suggest that CHM may play a role in the management of chemotherapy-induced toxicities. However, the current study has several intrinsic limitations, which compromise its scientific significance. For example, the authors did not conduct well-designed stratification analysis and the placebo used in this study contains medicinal tea (i.e. *Camellia sinensis*), so the conclusion appears unconvincing. A stratification analysis will check for the effects of other potential covariables such as age, gender, performance status, and tumour type and chemotherapy regimen on toxicity profiles. In particular, the choice of a placebo containing medicinal herbal components is unacceptable. In addition, the herbal treatment regimen was 14 days starting from day 1, which was not optimised. The study did not measure any biomarkers indicating the active components in the herbal formula probably responsible for its efficacy.

A potential pharmacokinetic response of anticancer drugs to herbal medicines should also be taken into account when CHM is used in combination with cytotoxic drugs. This occurs because herbal medicines alter the absorption, metabolism and disposition of chemotherapeutic drugs.[7,8] For example, St John's wort (*Hypericum perforatum*) has been found to reduce by 42% the plasma levels of SN-38, a cytotoxic metabolite of irinotecan used in the treatment of advanced colon cancer.[9] Two recent studies indicate that St John's wort treatment also significantly reduced the area under the plasma concentration time curve of imatinib (a potent inhibitor of the Bcr-Abl and c-kit tyrosine kinases) in healthy subjects.[10,11] In addition, garlic (*Allium sativum*) consumption decreases the systemic clearance of docetaxel in cancer patients harbouring a cytochrome P450 3A5 (*CYP3A5*1A*) allele.[12] Therefore, caution must be taken when herbal medicines are used with an attempt to ameliorate the toxicities of cancer chemotherapy.

CONCLUSION

Many cancer patients receive Chinese herbal medicines despite the lack of evidence supporting their potential beneficial effects. This certainly highlights the necessity of testing the efficacy and safety of Chinese herbal medicines aimed at reducing the host toxicities of chemotherapy.

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BOX 1 Two hundred and twenty-five commonly used herbs utilised in the study by Mok et al.[4]

Radix Scrophulariae (Xuanshen); Polyporus (Zhuling); Coix lacrymajobi (Yiyiren); Semen Plantaginis (Cheqianzi); Herba Lysimachiae (Jinqiancao); Spora Lygodii (Haijinsha); Herba Artemisiae scopariae (Yinchenhao); Fructus Kochiae (Difuzi); Herba Dianthi (Qumai); Herba Plantaginis (Cheqiancao); Pericarpium Arecae (Dafupi); Rhizoma Smilacis glabrae (Tufuling); processed Radix Aconiti (Caowu); Rhizoma Zingiberis (Ganjiang); Cinnamomum cassia; Herba Asari (Xixin); Fructus Evodiae (Wuzhuyu); Radix Aconiti kusnezoffii (Caowu); Citrus reticulata; Fructus Auranti immaturus; Citrus medica; Cyperus rotundus (Xiangfu); Radix Linderae strychnifoliae (Wuyao); Fructus Meliae toosendan (Chuanlianzi); Caulis Perillae (Sugeng); Massa medicata fermentata (Shenqu); Fructus Hordei germinatus (Maiya); Fructus Crataegi (Shanzha); Semen Raphani (Laifuzi); Herba seu Radix Cirsii japonici (Daji); Herba Cephalanoploris (Xiaoji); Radix Sanguisorbae (Diyu); Sophora japonica; Thuja orientalis; Herba Agrimoniae (Xiahecao); Rhizoma Bletillae (Baiji); Pollen Typhae (Puhuang); Radix Notoginseng (Sanqi); Rhizoma Ligustici (Chuanxiong); Olibanum (Ruxiang); Myrrha (Moyao); Rhizoma Corydelis (Yanhusuo); Radix Curcumae (Yulin); Rhizoma Curcumae (Ezhu); Rhizoma Sparganii (Sanleng); Radix Salviae miltiorrhizae (Danshen); Herba Leonuri (Yimucao); Semen Persicae (Taoren); Flos Carthami (Honghua); Faeces Trogopteri (Wulingzhi); Achyranthes bidentata (Huainiuxi); Cyathula officinalis (Chuanniuxi); Squama Manitis (Chuanshanjia); Lignum Dalbergiae odoriferae (Jiangxiang); Fructus Liquidambaris (Lulutong); processed Rhizoma Pinelliae; Rhizoma Pinelliae (Banxia); Rhizoma Arisaematis (Tiannanxing); Rhizoma Typhonii (Baifuzi); Radix Aconiti coreani; Radix Platycodi (Jiegeng); Flos Inulae (Xuanfuhua); Bulbus Fritillariae thunbergii (Zhebeimu); Rhizoma Cynanchi stauntonii (Baiqian); Fructus Trichosanthis (Gualou); Bulbus Fritillariae cirrhosae (Chuanbeimu); Caulis Bambusae in taeniis (Zhuru); Bitter Apricot Kernel (Kuxingren); Sargassum fusiforme; Radix Stemonae (Baebu); Loquat leaf (Pipaye); Radix Scutellariae (Huanqin); Cortex Mori albae radicis (Sangbaipi); Semen Lepidii (Tinglizi); Stir-baked Flos Tussilaginis farfarae (Kuandonghua); Radix Peucedani (Qianhu); Ferrosoferric Oxide; Os Draconis (Longgu); Semen Ziziphi spinosae (Suanzaoren); Semen Biotae (Baiziren); Radix Polygalae (Yuanzhi); Cortex Albizziae Hehuanpi); Radix Codonopsitis (Dangshen); Radix Pseudostellariae (Taizishen); Radix Astragali (Huangqi); Rhizoma Atractylodis macrocephalae (Baizhu); Rhizoma Dioscoreae (Bixie); Glycyrrhiza uralensis; Radix Panacis quinquefolii (Xiyangshen); Ziziphus jujuba (Dazao); Radix Morindae officinalis (Bajitian); Herba Cistanches (Roucongrong); Rhizoma Curculiginis (Xianmao); Herba Epimedii (Yinyanghuo); Cortex Eucommiae (Duzhong); Radix Dipsaci (Xuduan); Rhizoma Cibotii (Gouji); Rhizoma Drynariae (Gusuibu); Fructus Psoraleae (Buguzhi); Fructus Alpiniae oxyphyllae (Yizhiren); Cuscuta japonica; Herba Cynomorii (Suoyang); Radix Angelicae sinensis (Danggui); Rehmannia glutinosa; Radix Polygoni multiflori (Heshouwu); Radix Paeoniae albae; Radix Ophiopogonis (Maimendong); Herba Dendrobii (Shihu); Bulbus Lilii (Baihe); Fructus Lycii (Gouqizi); Herba Ecliptae (Hanliancao); Ligustrum lucidum; Radix Glehniae (Shashen); Fructus Schisandrae (Wuweizi); Fructus Tritici aestivi levis (Fuxiaomai); Radix Oryzae glutinosae; Radix Ephedrae (Mahuanggen); Fructus Corni (Shanzhuyu); Fructus Rosae laevigatae (Jinyingzi); Fructus Rubi (Fupenzi); Concha Arcae (Wanglengzi); Folium Ginseng; Radix Adenophorae (Nanshashen).

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Herbal Medicine for Depression

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Depression is one of the most common disorders for which treatment is sought through complementary therapies, including acupuncture and herbal medicine.[1,2] There are three very common types of depressive disorders: major depression (unipolar depression), dysthymia (a less severe depression), and bipolar disorder (manic-depressive illness).[3] Depression affects about 121 million people worldwide.[4] In any given one-year period, 9.5% of the population in the United States of America suffer from depression.[3] Depression falls into the category of *Yu* syndrome in traditional Chinese medicine (TCM) and its treatment depends on pattern differentiation. Liver Qi stagnation is one of the common patterns for depression. Herbal formulas containing *Chaihu* (*Radix Burpleuri*), which are also called *Chaihu Ji*, are often used for depression treatment. Recent research has examined the clinical effectiveness and biological mechanism of *Chaihu Ji* in the treatment of depression.

CLINICAL STUDY WITH *XIAO YAO SAN*

Zhang et al.[5] investigated the effect of *Jia Wei Xiao Yao San* (JWXY) as monotherapy in depressed patients. A total of 87 unipolar and 62 bipolar depressed patients were randomly assigned to treatment with 36 g/day JWXY (n = 86) or placebo (n = 63) for 12 weeks under double-blind conditions. Both unipolar and bipolar patients assigned to JWXY displayed significantly greater improvement on the three efficacy indices, i.e. the Hamilton Rating Scale for Depression, Montgomery-Asberg Depression Rating Scale, and Clinical Global Impression-Severity, and a significantly higher clinical response rate (74%) than those treated with placebo (42%, $p < 0.001$) at end point of 12 weeks.

In addition, this study also examined the effect of JWXY as adjunctive therapy with carbamazepine (CBZ) for bipolar disorders by using a double-blind, randomised, placebo-controlled method. Bipolar patients (n = 188) were treated by CBZ plus placebo (n = 92) or CBZ plus JWXY (n = 96) for 26 weeks. Patients taking adjunctive herbs showed a significantly lower overall discontinuation rate (31%) at end point compared to placebo (51%). Patients receiving adjunctive herbs had significantly fewer adverse side effects, such as dizziness and fatigue, and lower serum levels of CBZ than those in placebo. The combination of JWXY with CBZ resulted in significantly better outcomes on depressive measures at week 4 and week 8, but not in the later stage (from week 12 to week 26). The combination treatment failed to produce significantly greater improvement on manic measures. These results suggest that adjunctive JWXY improves tolerability of CBZ in long-term use. JWXY monotherapy may also be an effective alternative treatment for depressed conditions.

Chen et al.[6] studied the effects of *Xiao Yao San* in patients with the pattern of Liver-Qi stagnation and Spleen deficiency.

Fifty-eight cases were randomly divided into two groups: 41 cases in the experimental group were treated with *Xiao Yao San* and 17 cases in the control group were treated with *Zhi Bai Di Huang Wan* for one consecutive month in a single blind design. Before and after treatment, the changes of plasma norepinephrine (NE), epinephrine (E), dopamine (DA), β-endorphin (β-EP), adrenocorticotropin hormone (ACTH), estradiol (E2), testosterone (T), and immunoglobulin A (Ig A) and G (Ig G) were measured. These indices were used to determine the effect of herbs on neuron-endocrine and immune markers. Compared to baseline levels, plasma β-EP was significantly increased at one month, while E and DA were markedly decreased after the administration of *Xiao Yao San*. No effect was found on other study end points. These results suggest *Xiao Yao San* may work through enhancing plasma β-EP and decreasing E and DA release. *Xiao Yao San* may regulate nervous and endocrine systems and contributes to the improvement of the clinical status of patients with Liver stagnation and Spleen deficiency.

CHAIHU GUIZHI GANJIANG TANG IMPROVING DEPRESSED MOOD

Ushiroyama et al.[7] examined the effects of *Chaihu Guizhi Ganjiang Tang* (CGG) in 90 depressed peri- and post-menopausal women. The effect of CGG was examined in relation to improving depressed mood, and stress moderators cytokines interleukin-6 (IL-6), and interleukin-6 receptor (sIL-6R) concentrations. Subjects were separated into two groups (herb group 42 cases and anti-depressants group 48 cases). Plasma IL-6 and sIL-6R concentrations were determined before and after three months of the treatment. There were no significant reductions in both climacteric and Hamilton depression score after treatment between groups. Plasma IL-6 and sIL-6R concentrations were significantly lower in the herbal group (–34.8 ± 15.5% and –22.4 ± 14.6%, respectively) compared to the anti-depressant group (7.5 ± 4.8% and 2.4 ± 3.8%, respectively) after three months of treatment. CGG reduced plasma IL-6 and sIL-6R concentrations in relation to improvement of depressed mood during treatment. These findings suggest that CGG has the potential to decrease morbidity by alleviation of stress reactions in peri- and post-menopausal women.

LABORATORY STUDY WITH *CHAIHU JIA LONGGU MULI TANG*

Mizoguchi et al.[8] studied the effect of *Chaihu Jia Longgu Muli Tang* (CLM) on the chronic stress-induced changes in glucocorticoid receptors in the prefrontal cortex (PFC) and hippocampus, and disruption of the hypothalamo–pituitary–adrenal (HPA) axis. A reduction in glucocorticoid receptor (GR) function and dysfunction of the glucocorticoid negative feedback system were observed in human depressives. Previously, Mizoguchi et al. reported that chronic stress in rats induced a decrease of cytosolic GRs or increased nuclear GRs[9] and CLM prevented the chronic stress-induced HPA disruption.[10] In this study, chronic stress was induced in rats by water immersion and restraint (2 h/day) for four weeks. CLM significantly prevented decreased cytosolic GRs in the PFC and increased nuclear GRs in the hippocampus. Moreover, CLM significantly prevented the abolishment of feedback ability in both regions. These results suggest that the beneficial effects of CLM on the GR level are involved in its ameliorating actions on the HPA disruption. This finding provides information important for the prevention and treatment of depression.

Zhu et al.[11] investigated the antidepressant-like effect of saponins extracted from CLM in mice and rats using the tail suspension test (TST) and the forced swimming test (FST). Subchronic administration of 100 and 200 mg/kg (p.o.) of the extract for seven days reduced immobility time in the TST and FST in mice and also decreased immobility time at 70 and 140 mg/kg (p.o.) in the FST in rats. The results also showed that the anti-immobility activity of SCLM in these two tests is dose-dependent, without accompanying significant effects on locomotor activity. Experiments using PC12 cells suggest that the antidepressant-like effect of CLM might be mediated via the cytoprotective action.

CLINICAL RELEVANCE

The above studies from clinical trials, animal models, and laboratory examinations suggest that *Chaihu*-containing formulas (*Chaihu Ji*) may be effective in the treatment of depression. While *Chaihu Ji* includes several formulas with different herbal components, each formula is used for different patterns. Depression may be treated by different principles with different formulas. For the clinical application of *Chaihu Ji* in the treatment of depression, it is still necessary to apply treatment based on pattern differentiation.

CONCLUSION

The role of herbal medicine in the treatment of various psychological disorders including depression has become well established over the past decade.[1] Recent studies support the fact that herbal medicine may be an effective choice for the treatment of depression. The interaction of herbal medicine and conventional antidepressants is an important issue to be studied, although some research has been done in this field.[1,12,13]

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