



A narrative review of the immunomodulatory and anticancer activity of some components of Shi-Quan-Da-Bu-Tang

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Contributions: (I) Conception and design: All authors; (II) Administrative support: All authors; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Recently a lot of studies have indicated that in cancer treatment Chinese herbal medicines in combination with chemo-, radio-, or targeted-therapy can be useful to improve the efficaciousness of the therapies and decrease their side effects. Shi-quan-da-bu-tang (SQT) is a tonic decoction that greatly tonify blood and vital energy and ameliorate health and immunity. This powerful and traditional herbal blend has been used to improve weak constitution and general discomfort. Recent research have shown that SQT has relevant effect on decrease cancer-related fatigue and pain, ameliorating peripheral neuropathy and gastrointestinal side effects such as diarrhea, nausea, sickness, reduce the incidence of bone marrow suppression, block incidence of malignancies. This study wants to be a support to figure out the anticancer characteristics and the immunopotentiating effects (by triggering hematopoietic stem cells and interleukins production) of some medicinal herbs that compose SQT. Anyway further research need to be done to better understand cancer specific molecular therapy.

Keywords: Shi-Quan-Da-Bu-Tang; oncology; cancer; Chinese herbal medicines

Received: 08 November 2020; Accepted: 18 February 2021; Published: 30 March 2021.

doi: 10.21037/lcm-20-55

View this article at: <http://dx.doi.org/10.21037/lcm-20-55>

Introduction

Shi-quan-da-bu-tang (Juzentaiho-to in Japanese, or Sipjeondaebo-tang in Korean) is a famous Chinese herbal formulation first reported in the Chinese Song Dynasty (about A.D. 1,200).

The origin and the traditional use of Shi-Quan-Da-Bu-Tang (Juzen-taiho-to in Japanese) are found in a formula composed of ten crude drugs derived from the formula Si-Jun-Zi-Tang (Shikunshi-to in Japanese), which consists of four crude drugs (Ginseng Radix, Atractylodis Rhizoma, Poria, and Glycyrrhizae Radix) and another formula, Si-Wu-Tang (Shimotsu-to in Japanese), consisting of four crude drugs (Angelicae Radix, Paeoniae Radix, Liquisticum wallichii, and Rehmanniae Glutinosa) plus two additional

drugs: Cinnamomi Cortex and Astragali Radix, prescribed to improve the power of both formulas.

The formula Si-Jun-Zi-Tang was used to strengthen Qi and vital energy of the whole body and to counteract symptoms as the lack of energy and vigor, fatigue and anorexia. Si-Wu-Tang was prescribed to tonify blood and to fight signs such as dry skin, loss of hair, blurred vision (1).

Shi-Quan-Da-Bu-Tang (SQT) are generally administered as dried decoction.

Aim of the narrative review is the description of the scientific evidence of the anticancer characteristics and the immunopotentiating effects (by triggering hematopoietic stem cells and interleukins production) of some medicinal herbs that compose SQT.

We present the following article in accordance with the

Narrative Review reporting checklist (available at <http://dx.doi.org/10.21037/lcm-20-55>).

Methods

Key references were derived from a PubMed query (through September 30, 2020). Hand searching (including meeting proceedings) and clinicaltrials.gov were also used. Also, studies known to the authors, as well as references from the identified studies, were further examined.

Only English written publications were selected, with no limitations for “Publication years”.

Articles were obtained using the combination of the following keywords: “Shi-Quan-Da-Bu-Tang”, “oncology”, “cancer”, “SQT”.

IB and GM independently extracted data from each study. Disagreements were resolved by discussion between reviewers (IB, GM, VN). Results were summarized and discussed narratively.

Body: components of SQT and their immunomodulatory and anticancer activity

In this study it will be analyzed the properties of some components of SQT and in particular, their anticancer and immunomodulating activity (2) (see *Table 1*).

Rehmania glutinosa (RHG). RHG is one of the most efficacious blood and kidney tonics and TCM is said to extend the life: “calm the soul, and confirm the spirit”. RHG is used as a tonic, an anti-aenemic and a fever-reducing. *Rehmania glutinosa* polysaccharide (RGP) has revealed an immune stimulatory effect (3).

The polysaccharide fraction has been shown to improve non-specific immunity and cell immunity mediated by the activation of T lymphocytes. Furthermore, the polysaccharides have been shown to increase the activity of the reticular-endothelial system whose role is to remove foreign substances out of the body (4).

Researchers investigated the effects of *Rehmania glutinosa* steamed root (RGAE) in type I hypersensitivity reactions showing a dose-dependent inhibition of histamine release *in vivo* and *in vitro* and inhibition of TNF- α production. Then the anti-inflammatory activity of *Rehmania* in the central nervous system was highlighted, showing that RGAE inhibits TNF- α secretion, blocking IL-1 production in astrocytes activated with lipopolysaccharides. These data demonstrate that RGP could be a useful adjuvant molecule to modulate immune

and inflammatory response (5).

RGP has shown also an anticancer activity: RGP polysaccharide inhibited the tumor growth in the lung of mice *in vivo* by activating natural killer cells.

Another study demonstrates that RGP is a dendritic cell maturation reagent as an adjuvant that can induce Ag-specific Th1 and CTL (cytotoxic T lymphocytes) activation, which consequently stimulates the inhibition of As-expressing tumor growth, including B16 melanoma and CT26 carcinoma cells *in vivo*. Thus, the RGP will be a hopeful candidate for developing an immunotherapy reagent for human uses against cancer (15).

Atractylodes macrocephala (Bai-zhu in Chinese) is a medicinal plant that has been used, since long time, as a tonic-stimulating agent in various country in East Asia, especially in China. The methods of Chinese medicine processing became more and more usual after the Song Dynasty. The crude *A. macrocephala* (CA) and bran-processed *A. macrocephala* (BA) are the two drugs that are prepared and used widely in China. Medically, the CA is mainly used to eliminate damp in the Middle-Jao and diuresis while after bran-processed can significantly ease dryness and tonify Qi and spleen.

Atractylone, the main compound of CA and BA, can reduce allergic rhinitis (AR) clinical symptoms and biomarkers including total IgE, histamine, prostaglandin D2, tumor necrosis factor- α , interleukin (IL)-1 β , IL-4, IL-5, IL-6 having said that, atractylone is a potential therapeutic agent for AR and has a good immune and anti-inflammatory activity (6).

Atractylenolide (ATR 1): an active component of *Rhizoma Atractylodis* is particularly effective against various types of cancer: recent studies have shown that ATR1 blocks bladder cancer cell growth, inhibits the cell cycle in G2/M phase with up- regulation of p21 and down-regulation of cyclin B1 (16).

Atractylodes combined with Ginseng Radix and *Poria cocos* (SGE) is used as an anti-cancer coadjuvant to treat cachexia, characterized by unintentional weight and muscle loss. In some *in vitro* experiments SGE the proliferation of CT-26 murine colon carcinoma cells have been also blocked with endoplasmic reticulum stress (7).

Poria cocos (Fu-lin in Chinese) is an important medicinal fungus used in China for centuries. The chemical composition of *Poria cocos* includes triterpenoids, polysaccharides, steroids, choline. Triterpenoids are known to have a great effectiveness on certain diseases such as rheumatoid arthritis, psoriasis, autoimmune uveitis, while

Table 1 Summary table of the seven-herb mixture of Shi-Quan-Da-Bu-Tang and actions of each component

Chinese name	Latin name	Biological activity	Clinical evidence of anticancer activity
Shu-di	<i>Rehmania glutinosa</i> (RHG)	Antitumor, immunomodulation, antimutagenicity (3,4)	<i>Rehmania glutinosa</i> polysaccharides inhibit the tumor growth by activating natural killer cells (5)
Bai-Zhu	<i>Atractylodes macrocephala</i> (AMC)	Enhancement of humoral, cellular immunity and peripheral NK cells. Anti-inflammatory activity (6)	Active component of <i>Rhizoma Atractylodis</i> blocks bladder cancer cell growth (7)
Fu-lin	<i>Poria Cocos</i> (POC)	Immunomodulators properties: enhancement of immune stimulator and lowering of immune suppressor (8)	<i>Poria Cocos</i> in combination with oxaliplatin inhibits the proliferation of gastric cancer cells (9)
Dang-gui	<i>Angelica sinensis</i> (AGS)	Anti-inflammatory, analgesic, antispasmodic. Effective in treating signs of blood deficiencies	Antitumor effects in liver, oral and lung cancer
Bai-shao	<i>Paeonia Lactiflora</i> (PL)	Anti-inflammatory and immunomodulatory properties. Useful to treat autoimmune disease (10)	PL is good to treat anorexia/cachexia (11). Effective in inhibiting pancreatic cell growth (12)
Ren-shen	<i>Panax ginseng</i> (PGS)	Antioxidative, hepatoprotective, anti-inflammatory effects (13)	Many components of PGS (polysaccharides, ginsenosides, peptides) have anticancer activity (14)

polysaccharides can boost the immune response (8).

Poria Cocos has immunomodulators properties: it modulates the immune function through the effective regulation of cytokines.

A study showed that Fu-Ling extract enhanced the secretion of immune stimulators (IL-II3, IL-6 and TNF- α) but suppressed the secretion of an immune suppressor (TGF-13), the substance in 50% hot ethanol extract of Fu-Ling might have potentiated the immune response. However, in another experiment it was found that *Poria Cocos* represses the secretion of transforming growth factor (TGF)- β . The increased secretion of IL-1 β , IL-6, and TNF- α by activated macrophages strengthens the immune response. The inflammatory response is also connected to high levels of these three cytokines in serum secreted by activated neutrophils, because these three cytokines, which are secreted by activated neutrophils and which promote the mononuclear phagocytes, are implicated in fever and the acute phase of inflammation. TGF- β quells instead, the inflammatory response by hindering macrophage trigger and the secretion of other cytokines. The extract of *Poria cocos* strengthen the secretion of immune stimulators (IL-1 β , IL-6, and TNF- α) and suppresses the secretion of an immune suppressor (TGF- β). It should be useful to boost immunity system (17).

Poria cocos has also anticancer activity. PC contains pachymic acid (PA), a lanostane-type triterpenoid that

hinders production of the phospholipase A2 (PLA2), enzyme significantly elevated in prostatic cancer cells. PA induced apoptosis of the cells through mitochondria dysfunction activating caspases 9 and 3. Other studies suggest that *Poria Cocos* in combination with oxaliplatin inhibits the proliferation of gastric cancer cells blocking the epithelial-mesenchymal transition process (9). Moreover, as one of the most commonly used herbs combined with the FOLFOX4 chemotherapy regimen that could successfully ameliorate tumor response rate, survival and quality of life (QOL) of patients and promote reduction of adverse effects (18).

Angelicae Sinensis Radix (AS): commonly known as Dong-quai (in Chinese), is a drug belonging to the family Apiaceae. Phytochemical studies have shown that the major constituents of AS (phytosterols, polysaccharides, ligustilide, butylphthalide, cnidilide) have a variety of pharmacological effects such as anti-inflammatory, analgesic, antispasmodic. Moreover, in traditional Chinese medicine AS is used to tonify blood in liver and hearth, and to treat signs of blood deficiencies such as anemia, pallor, fragile nails, hair dry. It is also useful to cure gynecological disorders (it has been called "female ginseng") such as premenstrual syndrome, irregular menstrual cycle, dysmenorrhea, menopausal symptoms. Some reports indicated that bioactive phtalides from AS have neuroprotective effects. Phtalides fight the neurotoxicity of glutamate, involved in neurodegenerative

diseases (Parkinson's disease, Alzheimer's disease and amyotrophic lateral sclerosis) (19).

Moreover, some studies indicated that AS and some of its active constituents exhibited great anticancer effects in liver, oral, and lung cancers leading apoptosis, controlling multidrug resistance (MDR), balancing lymphocyte activity and boosting immune system. Two compounds isolated from AS had an inhibitory effect on glutathione S-transferase (GST). GST with multidrug resistance is considered an impediment to the realization of a good cancer chemotherapy (20).

In addition, ultra-filtration extract (RAS-RH) of Radix Angelicae Sinensis and Radix Hedysari could increase radiosensitivity of radiation in human liver cancer cells H22 by regulating apoptosis protein (21).

Paeonia Lactiflora (PL) (Bai-shao in Chinese): in traditional Chinese Medicine, PL has been used to reduce inflammation, to treat immune disorders for more than 1,200 years in China. It is effective in treating dizziness, cramp, engorgement and gynecological disorders. Total glycoside of paeony (TGP) is extracted from the dried root of *Paeonia lactiflora*. TGP has been used in China to treat autoimmune diseases, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), psoriasis, allergic contact dermatitis, and etc. (10). Paeoniflorin (Pae) is the major active component of TGP. Pae has anti-inflammatory and immunomodulatory properties. Pae could repress inflammation in the animal models of autoimmune diseases (psoriasis, rheumatoid arthritis). It regulates the function and triggering of immune cells, lowers inflammation, adjusts signaling pathway. This suggests that TGP could be a hopeful anti-inflammatory and immune drug and useful to treat autoimmune diseases systemic lupus erythematosus (SLE), psoriasis, allergic contact dermatitis. Moreover, a study demonstrated that TGP suppressed lipopolysaccharide (LPS)-stimulated proliferation, migration and invasion in androgen insensitive prostate cancer cells (22).

Recently it has been shown that Radix *Paeonia* (RP) could inhibit cancer anorexia/cachexia. In particular, *Paeonia* root extract blocked the loss of skeletal muscle function and prevented anorexia slowing down NF- κ B signalling and muscle-specific E3 ubiquitin ligases (11).

Another study demonstrated that PF blocked growth of some pancreatic cell lines and deeply sensitized these cells to X-ray irradiation by increasing HTRA3 (protein belongs to the highly conserved HtrA family of stress-related serine proteases) expression and promoting HTRA3-mediated apoptosis (12).

Ginseng Radix is the root of *Panax Ginseng* (Ren-shen in Chinese) which has origin in northern China, Korea and northeastern Russia. It is one of most famous crude drugs and is used as a tonic, preventive, replenishing agent in Chinese traditional medicine. *Panax* is derived from *Panacea*, that means "longevity". It is classified as a tonic and adaptogen because some studies in animals have revealed that it could help the body fit to stress and make up for adrenal and thyroid dysfunction.

Ginseng has antistress activity and positive action on metabolism, the central nervous system and endocrine secretion. It is used in Orient for the treatment of anemia, diabetes, gastritis, asthenia, dyspepsia.

A lot of pharmacological researches has demonstrated that *Panax Ginseng* has a wide variety of benefits on human health such as immunomodulatory activity, antitumor effect, such as antioxidative, hepatoprotective, anti-inflammatory effects (13).

Panax ginseng contains many active components such as ginsenosides, peptides, essential oil and polysaccharides, among which, ginsenosides (e.g., Rg3 and Rb1) are considered an excellent choice for their anticancer activity.

A case-control study conducted in the Korea Cancer Center Hospital underlined that patients taking ginseng had a 50% less risk of cancer recurrence respect to patients not taking ginseng (14). Another review addressed the question of the radioprotective effects of ginseng on mammalian cells both *in vitro* and *in vivo*. Results indicate that the extract of whole ginseng seems to give a protection against radiation-induced DNA damage and in conclusion this drug appears to be an excellent radio-protector for treatment protocols able to mitigate damaging effect of radiation on human tissue, particularly for patients who need radiotherapy (23). It could ameliorate radiation-induced liver injury, which might be related with the modulation of oxidative stress, inflammatory reactions, and apoptosis (24).

Ginsenoside Rg3 is one of active pharmaceutical ingredients (steroidal saponin) extracted from the traditional Chinese medicine ginseng which is regularly used to improve immunity in TCM. Rg3 has been shown to have a variety of effects, including anti-viral (25), anti-obese (26), anti-hypertrophic scars. *Panax Ginseng* is usually recommended to boost immunity guided by the guidelines of TCM, and it has been confirmed that Rg3 could also normalize the ratio of CD4 and CD8T cells in NSCLC (non-small cell lung cancer) patients (27).

Moreover, Rg3 also shows multiple antitumor effects, such as furthering cytotoxicity of chemotherapy in breast

cancer (28), blocking epithelial-mesenchymal transition (EMT) in lung cancer (29), triggering autophagy in ovarian cancer (30).

A prospective randomized controlled study has showed that Rg3 could ameliorate the efficacy of chemotherapy and postpone the drug resistance for treatment of advanced NSCLC (31). Another study affirmed that Ginsenoside Rg3 could be a novel agent targeting programmed death ligand 1 (PD-L1) in treating chemotherapy refractory NSCLC (32). A large sample, randomized clinical trial on ameliorating the average survival time of advanced non-small cell lung cancer by combination of Ginseng Rg3 and chemotherapy was executed by Zhang *et al.* They underlined that a combination of Ginsenoside Rg3 with chemotherapy could increase survival of patients with advanced NSCLC, better patients' symptoms and decrease chemotherapy induced myelosuppression (33).

Astragali radix (Huang Qi) is one of the most known herbal medicine and has a long history of medicinal use in TCM and salutary food supplement used as a tonic, and it is classified under the group of "Qi" tonifying drugs. It has been considered as a tonic with the quality of spiriting vital energy which presents symptoms such as anorexia, chronic diarrhea, exhaustion, menorrhagia. used to strengthen Qi, to ameliorate vital energy and to stimulate the discharge of pus and new tissue growth. Widely used also to boost a naturally delicate constitution and to balance bad nutrition. Saponins, flavonoids and polisaccharides are the mayor constituents of Astragali Radix (RA).

Polysaccharides and saponins are biological components known for anticancer and immunostimulating properties. Recent studies have shown that RA can be useful to treat chemotherapy induced perypheral neuropathy (CIPN) caused by toxic effects of chemoterapy drugs. This neuropathy is very crippling for the patients. RA has the property to relieve symptoms, improve quality of life and immunological function and delay the spread of CIPN (34). Astragalus has been also used to raise the body's defenses and to increase the number of blood cells in lymphatic tissue and bone marrow and from here promote the growth into active immune cells (35). It has boosted the natural killer (NK) cell activity of peripheral blood lymphocytes and reestablishes NK cell activity inhibited by steroidal drugs.

Summary and conclusions

In TCM, some specific herbs, minerals and combination

formulas were collected and used due to their active principles and specific natural compounds with antitumor activities. Shi-Quan-Da-Bu-Tang has a synergistic and regulatory effect, with few side effects. Its components have shown valid efficacy in potentiating results of chemotherapy and radiotherapy, in triggering hemopoietic and interleukin activity and improving side effects (nausea, vomit, dyspepsia, hematotoxicity) of anti-cancer substances.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at <http://dx.doi.org/10.21037/lcm-20-55>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/lcm-20-55>). VN serves as an unpaid editorial board member of *Longhua Chinese Medicine* from Aug 2020 to Jul 2022. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/lcm-20-55

Cite this article as: Bisogno I, Musumeci G, Nardone V. A narrative review of the immunomodulatory and anticancer activity of some components of Shi-Quan-Da-Bu-Tang. *Longhua Chin Med* 2021;4:4.