

## Principles and Scientific Basis of Traditional Chinese Medicine in Cancer Treatment

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### Abstract

Traditional Chinese Medicine (TCM) have been used to reduce toxic effects and enhance therapeutic effects of modern cancer therapy, palliate clinical syndrome or improve quality of life, enhance immune function, prevent recurrence and metastasis, and anti-cancer therapy for patients failed in or refuse to conventional treatment. From TCM perspective, the pathogenesis of cancer is related to weakened body resistance, blood stasis, phlegm stagnation and toxicity accumulation, and cancer are recognized as syndrome of blood-stasis, phlegm and toxicity in TCM. Syndrome Differential Treatment is the basic principle for cancer treatment. Anti-cancer effects of Chinese herb are associated with apoptosis, cell senescence, autophagy and other mechanisms. Chinese herbal formula is the major application form of Chinese herb. Most TCM physicians prescribe or combine multiple herbs for a formula or prescription based on TCM principles, pharmacological progression and personal experience. We emphasize application of anti-cancer herb must guided by TCM principles. There is a great need to explore the combination rule of anti-cancer herbs, and establish effective herbal formulas for various situations in cancer treatment.

**Keywords:** Cancer; Traditional Chinese medicine; pathogenesis; Chinese herbal formula; effective mechanisms

### Introduction

Cancer has become the global healthy problem. According to global statistics, 12.7 million cancer cases and 7.6 million cancer deaths occurred in 2008 worldwide [1]. For most cancer patients, surgery, radiotherapy and chemotherapy are the main conventional therapies. In recent years, accumulated investigations are focus on cancer biological therapies such as immunotherapy, gene therapy, and targeted therapy. These therapies are expensive and unbearable for some patients due to serious side effects. Cancer remains the leading cause of death in economically developed countries and the second leading cause of death in developing countries [2]. There is a great need to develop new approach for cancer prevention and treatment. Ethnomedicine, including Traditional Chinese Medicine (TCM), may provide new contribution to cancer treatment.

### Understanding of Traditional Chinese Medicine in Cancer

In china, TCM have long been used for treatment of various diseases including cancer. The word cancer was first described in inscriptions on bones or tortoise shells in the Shang dynasty (6<sup>th</sup>-11<sup>th</sup> century BC). Cancer related clinical manifestation and causes have been well described in Chinese medical literature since 400 BC [3]. As a malignant lesion, cancer was first appeared in the book of Wei-Ji-Bao-Shu (AD 1170). Cancer was well described by Yang SY, a famous doctor in the Song dynasty, in the book of Ren-Zhai-Zhi-Zhi-Fu-Yi-Fang-Lun (AD 1264), which described them as masses that were rock-firm and had uneven surfaces. As a new discipline, TCM oncology was rapidly developed in recent 60 years.

Holistic view is the basic characteristic of TCM. From TCM perspective, cancer is a systemic disease and the uncontrolled growth of tumor mass is only part of the whole sophisticated manifestations. Cancer patients also have certain body dysfunctions and even meridian disorders, and show different TCM syndromes. TCM believes a weakened body anti-disease capabilities (vital Qi) is the basis of

carcinogenesis, which makes individuals susceptible to different carcinogenic factors, such as environment and diet factors. In addition to extrinsic carcinogenic factors, congenital deficiencies, emotional stress and lifestyle and also play a role in carcinogenesis. Body and carcinogenic factor interaction result in internal disharmony, and leading to accumulation of pathological products, such as blood-stasis, phlegm and toxicity. Qi-stagnation and Blood-stasis, phlegm retention and toxicity accumulation are the general pathological characteristics of all cancers [3-7]. The cancer progression due to the body anti-disease capabilities (vital Qi) can't eliminate pathological products timely. Cancer can be healing with promoting body resistance and eliminating pathological products.

### Present Situation of TCM in Cancer Treatment

Present in China, every province or municipalities possess one or more professional TCM oncology department in TCM hospital, and all professional cancer hospital possess a TCM oncology department. TCM, as a patient-tailored ethnomedicine, was used in almost all cancer patients in China. Over a long-term practice, TCM has accumulated various methods for cancer treatment, such as Chinese herb, acupuncture and moxibustion, and Qi Gong. TCM have been integrated to modern comprehensive therapy during the past 60 years due to the changes of cancer therapeutic model. At present, TCM have been widely used to reduce toxic side effects and enhance effects of

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modern therapeutics, palliate clinical syndrome or improve quality of life, enhance immune function, prevent recurrence and metastasis, and the last hope for patients failed in or refuse to conventional treatment. However, anti-cancer is the most common reason for patients to seek TCM treatment.

### Syndrome Differential Treatment in Cancer

In Traditional Chinese Medicine, “treatment according to syndrome differentiation” is the basic principle for all clinical applications. Based on patient’s condition and their different phases of cancer, TCM use its unique examination techniques and theories, then make diagnosis and select appropriate treatment method(s) as well as predict prognosis for each cancer patient. According to different TCM syndrome of cancer patients, TCM physicians may employ different Chinese herbs, acupuncture and moxibustion, or Qi Gong for cancer treatment. Chinese herbs are the major approach for anti-cancer or symptomatic treatment. Under the guidance of Syndrome Differential Treatment, patients with different cancers but have the same syndrome can be treated by the same TCM treatment law. However, one TCM treatment law may include different herbs with similar efficacy. Such as Panax Ginseng, Astragalus Membranaceus and Atractylodes Rhizome can be assigned to Qi-tonifying herbs, and Barbed Skullcap, Oldenlandia Diffusa and Rhizoma Pardis can be assigned to heat-clearing and detoxifying anti-cancer herbs. On the other hand, different treatment law will be adopted in patients with same cancer but different syndrome. These are just the theories of “same treatment for different disease” and “same disease treatment with different methods” in TCM.

For example, as a splenic Qi-tonifying herb, Atractylodes Rhizome can be used for all cancer patients with splenic qi-deficiency. As a Qi and blood-tonifying herb formula, Dang-Gui-Bu-Xue-Tang, an ancient herb formula, can be prescribed to all cancer patients with Qi and blood-deficiency to improve bone marrow hematopoietic function. In primary hepatocarcinoma patients, based on different syndrome patterns, physicians may employ invigorating spleen and regulating Qi, clearing heat-dampness, dissipating stasis, softening hardness, or tonifying liver and kidney to cure cancer [8-11]. TCM syndrome differentiation treatment also acts an important role in treating adverse effects caused by radio- or chemotherapy [12]. Syndrome Differential Treatment is the essential principle of TCM in cancer treatment.

### Possible Relationship between TCM Syndrome and Modern Medicine

It has been reported different stage of cancer, pathological type and even treatment may influence TCM syndrome distribution. Such as in Guangzhou area, spleen deficiency and Qi stagnation syndrome, Qi stagnation and blood stasis syndrome, spleen deficiency and damp-heat syndrome, and deficiency in liver and spleen syndrome are frequently observed in patients with stage II liver cancer. Liver and kidney Yin deficiency is the most common syndrome in patients with stage III liver cancer [13]. In gastric carcinoma, different TCM syndromes were related with gender, pathology, cell differentiation, infiltration depth, lymphaden metastasis, distant metastasis, and TNM stage. The common syndromes in female patients with gastric carcinoma were disharmony between liver and stomach, Yin impairment due to stomach heat, and insufficiency of both Qi and blood; while in males, interior retention of stagnant toxin, interior retention of phlegm and dampness, and deficiency-cold in spleen and stomach were common [15]. In lung cancer patients, deficiency of Qi, blood stasis,

damp-phlegm and deficiency of Yin are main syndromes of TCM in adenocarcinoma and squamous carcinoma [14].

In addition, some genes may relate to differential syndrome. C-erb-B2, an important prognostic factor in breast cancer, has been reported highly expressed in breast cancer patients with blood stasis syndrome than the other syndromes [16]. In gastric carcinoma, the expression of E-cad was significantly higher in stomach heat due to yin deficiency and exhaustion of both Qi and blood than in other syndromes. The level of MMP2 expression was markedly lower in incoordination between liver and stomach, stomach heat due to Yin deficiency, and insufficiency of spleen and stomach than that in retention of blood stasis toxin in the interior [17]. In lung cancer, genotypes of CYP1A1 MspI were reported associated to different TCM syndrome. The frequencies of CC genotype in essence and Qi deficiency syndrome were higher than that in other syndromes. CT was the main genotype in internal accumulation of phlegm-heat syndrome, while in internal heat due to Yin-deficiency syndrome CC was the main genotype [18].

Despite of endeavors were undertaken to explore the possible relationship between TCM syndrome and modern medicine. Current accumulated evidences are very preliminary; there is a long way to elucidate the factors that influence TCM syndrome formation and evolution, understand the possible scientific basis of TCM syndrome, translate opaque TCM theory and terminology into straightforward modern biomedical language, better guide TCM clinical practice of oncology, and ultimately improve TCM clinical efficacy in cancer treatment.

### Clinical Efficacy of TCM in Cancer Treatment

During conventional chemotherapy, radiotherapy or targeted therapy, toxic side effects such as emaciation, fatigue, hair loss, rash, nausea, vomiting, diarrhea and leucocytopenia still bedevil patients. To relieve these symptoms is one of the most common reasons for cancer patients to seek TCM treatment in China. Clinical data shown TCM have a clear advantage in dealing with these symptoms. A double-blind placebo-controlled randomized clinical study confirmed Chinese herbal medicine does have a significant impact on control of chemotherapy associated nausea [19]. Rheidola algida can improve chemotherapy-induced oral mucositis in breast cancer patients [20]. Bojungikki-tang may bring beneficial effects to cancer-related fatigue and quality of life in cancer patients [21]. A prospective randomized controlled study indicated that, combined with chemotherapeutic agents combining iodized oil chemo-embolization, Chinese medicine comprehensive therapy could extend the pain-relieving sustained time, improve quality of live and long-term survival with less adverse reaction in primary hepatic carcinoma patients [22]. Modified Sijunzi Decoction may reduce chemotherapy elicited leucocytopenia, nausea and vomiting in colorectal cancer patients undergoing FOLFOX4 chemotherapy [23].

Chinese herbal formula, as a major application form of Chinese herb, has showed synergistic effect with conventional treatment. Yang Wei Kang Liu, a modern herbal formula, combination with chemotherapy significantly increased the survival of stage IV gastric cancer patients, and may related to activation of major pro-apoptotic pathways in gastric cancer cells [24]. Combination transcatheter arterial chemoembolization and Jiedufang significantly prolonged survival of patients from 5.87 months to 9.2 months in unresectable hepatocellular carcinoma patients [25]. For advanced breast cancer, Shengqi Fuzheng,

a multiple-herb injection, can alleviate the bone marrow inhibition caused by chemotherapy, improve clinical symptoms and quality of life, and prolong the survival time, so as to enhance the efficacy of chemotherapy [26]. Shengqi Fuzheng is also effective in increase efficacy and reduce toxicity when combined with platinum-based chemotherapy for advanced NSCLC [27]. A retrospective analysis and comparison suggested treatment of senile advanced NSCLC with TCM alone has its apparent superiority in stabilizing tumor focus, improving clinical symptoms, elevating quality of life and prolonging the survival time [28].

In addition, Chinese herbal formula has been reported to be effective in prevent cancer metastasis. Invigorating spleen herb formula showed significantly effects to prevent metastasis in postoperative gastric cancer patient [29]. Weining herbal granules combined with chemotherapy also inhibited recurrence and metastasis in postoperative gastric cancer [30]. Fuzheng and Quxie herbal capsule applying in the succedent consolidating treatment for stage II and III colorectal cancer after radical operation might be favorable to reduce relapse and metastasis and improve quality of life [31]. While new drugs and approaches are being developed, combination with conventional therapies, TCM may provide new contribution to cancer treatment.

### Therapeutic Mechanisms of TCM against Cancer

Same with current pharmacotherapy, Chinese herbs act on cancer cells through apoptosis, cell senescence, autophagy and other mechanisms to achieve therapeutic effects [32-33]. Apoptosis, an evolutionarily conserved cell suicide process, is major mechanism in Chinese herb treatment. It have been reported cantharidin and *Curcuma aromatica* extract may induce apoptosis and G2/M cell cycle arrest in colorectal cancer cells, and related to caspase activation and cell cycle regulatory proteins [34-35]. *Spatholobus suberectus*, an herb widely used in cancer treatment, inhibits cancer cell growth by inducing apoptosis and arresting cell cycle at G2/M checkpoint, and associated with DNA damage and activation of phosphor-Chk1/Chk2 [36]. Chan-Yu-Bao-Yuan-Tang, a Chinese herbal formula, induces apoptosis in lung cancer cells via a mitochondria-mediated pathway [37]. Rhein, an anthraquinone compound isolated from *Rhubarb*, may induce apoptosis through the endoplasmic reticulum stress, caspase- and mitochondria-dependent pathways in human tongue squamous cancer cells [38].

Cell senescence, a state of stable irreversible cell cycle arrest provoked by a variety of stimuli, also contributes to herbal therapeutic response. Ganoderiol F, a tetracyclic triterpene isolated from *Ganoderma amboinense*, has reported to induce cell senescence in hepatoma HepG2 cells accompanied by activation of the mitogen-activated protein kinase EKR and up-regulation of cyclin-dependent kinase inhibitor p16 [39]. Resveratrol, a polyphenol component of *Polygonum cuspidatum* and grapes, may induce cell senescence with attenuated mono-ubiquitination of histone H2B in glioma cells [40]. Chronic treatment with subapoptotic concentration of resveratrol may induce p53 and p21 dependent cell senescence in colorectal carcinoma cells, and related to increased level of reactive oxygen species [41]. Tenglong Buzhong Decoction, a Chinese herbal formula, is effective in induce cell senescence in colorectal carcinoma cells, which related to up-regulation of p21 and p16, and down-regulation of RB phosphorylation [42].

Autophagy, an evolutionarily conserved self-defense mechanism in which organelles and proteins are sequestered and subsequently

degraded through fusion with lysosomes, has been recognized as a target for cancer treatment [43]. *Licorice Glycyrrhiza glabra* and its component licochalcone-A can induce autophagy in addition to apoptosis in human prostate cancer cells, accompanied by down-regulation of Bcl-2 and inhibition of the mammalian target of rapamycin (mTOR) pathway [44]. *G. lucidum* triterpene extract induced autophagy in colon cancer through the inhibition of p38 mitogen-activated kinase [45]. Bufalin, a major digoxin-like immunoreactive component of the Chinese medicine *Chansu*, could induce autophagy-mediated cell death in human colon cancer cells through reactive oxygen species generation and JNK activation [46].

In addition to direct against cancer cell, anti-angiogenesis also participate to Chinese herb elicited anti-cancer effects. Pang et al. reported that acetyl-11-keto-beta-boswellic acid, an active component of *Boswellia serrata*, strongly inhibits human prostate tumor growth by suppressing VEGFR-2 mediated angiogenesis [47]. Curcumin, a component of *Curcuma aromatica* and *Curcuma longa*, could inhibit angiogenesis in multiple tumor models [48-51]. Tanshinone I, a component of *Salvia Miltiorrhiza*, showed potent anti-angiogenesis activity in prostate cancer [52]. Decursin and decursinol angelate, ingredients isolated from *Angelica gigas*, possess potential to inhibit VEGF-induced angiogenesis via suppression of the VEGFR-2 signaling pathway [53].

Furthermore, Chinese herb has been reported effective in cancer prevention. Hochu-ekki-to (*Bu-Zhong-Yi-Qi-Tang* in Chinese), a classical Chinese herbal formula, may inhibit endometrial carcinogenesis induced by N-methyl-N-nitrosourea and 17beta-estradiol in mice [54]. Kurashige et al. reported *Astragalus* extract exerts an anticarcinogenic effect in carcinogen-treated mice through activation of cytotoxic activity and the production of cytokines [55]. Adlay bran and its ethanolic extract and residue may inhibit colonic carcinogenesis in rats [56].

### Chinese Herbal Formula for Cancer Treatment

In Chinese herbalism, every herb has its own characteristics, TCM physicians believe that illness can be effectively treated by combining herbs based on their various features. Combinations of multiple herbs guided by TCM theories, called Chinese herbal formula, are the major application form of Chinese herb. Generally, Chinese herbal formula is prescribed according to patient's body condition based on a careful differential diagnosis. But considered the special characters of cancer cells such as sustaining proliferation, immortal replication [57], TCM physicians always tend to select herbs with anti-cancer activities in Chinese herbal formula based on pharmacological studies or personal experience.

Ancient Chinese herbal formula with tumoricidal herbs can be preliminary consider as an anti-cancer formula. Such as *San-Huang-Xie-Xin-Tang* and *Huang-lian-jie-du-tang*, which contained *Rhizoma Coptis* with anticancer potential could inhibit the growth of human liver cancer cells [58-59], can be used in cancer patient with corresponding syndrome. Due to the lack of appropriate ancient Chinese herbal formula for cancer, most TCM physicians extemporaneously combine multiple herbs for a formula or prescription based on TCM principles, progress in the pharmacological studies and personal experience. However, there are a certain consensus, such as in lung cancer, *Pi invigorating* and *phlegm removing* method are the basic treatment method, and as anti-cancer herb, *Smilacis Glabra*, *Rhizoma Smilacis Glabrae*, *Herba Hedyotis Diffusae*, *Herba Scutellariae Barbatae* were

frequently used by experts [60]. All herbs prescribed for a formula are used on the guidance of monarch, minister, assistant and guide theory. Usually, an anti-cancer herbal formula contains 3-5 herbs against cancer, and others used to enhance anti-cancer effects, ameliorate syndrome or symptoms, or reduce possible adverse reactions induced by used herbs, and totally up to 12-20 herbs for a prescription.

In addition to pharmacological synergy or antagonism between herbs or herbal components [61,62], pharmacokinetic mechanism may contribute to herb-herb interaction. In co-decoction, different combinations may influence herbal chemical components [63,64]. It has been proved intra-herb pharmacokinetics interaction between quercetin and isorhamnetin, co-transporting with each other across Caco-2 cells monolayer, the permeability ratio of isorhamnetin and quercetin increased by 4.3 and 2.2 times [65]. Both total coumarins and volatile oil, two main components of *Radix Angelicae dahuricae*, could improve the intestinal absorption of baicalin *in vivo*, and had synergistic action to enhance absorption of baicalin [66]. Although there is a concern about herb-drug interaction in chemotherapy, a literature analysis suggested most of concerns appears to be theoretical [67], and needs to be further explored. However, there is a lack of pharmacokinetic investigation about anti-cancer herbs.

Most of clinical used herbs are safety, and have been used for thousands of years. Some herbs or minerals are toxic or have predictable side effects, and have been recorded in Chinese medical literature since 100 BC, such as toad venom, croton tiglium, monkshood, realgar. TCM has developed special herb processing methods and combination rules to avoid or reduce adverse reaction. It has been reported over 90% of adverse reactions induced by herbs are owing to overdose, improper or without processing, incorrect usage of toxic drug, the confused resource or misuse of medicinal plants [68]. A few of anti-cancer herbs or Chinese Traditional Patent Medicines have certain side effects, such as pepperbox, *solanum dulcamara*, pleione rhizome and compound capsules cantharidin, it is important to use these herbs under the guidance of TCM theories.

There is a great need to explore the compatibility or combination rule of herbs, understand herb-herb interaction, especially anti-cancer herb-herb interaction [61]. We has purposed a syndrome differential anti-cancer and scientific anti-cancer therapeutic model, in which application of all anti-cancer herb must firstly consider its property of Chinese herb and guided by TCM theories, and in the case of herb prescription under traditional thought, herbs with anti-cancer potential can be firstly considered [69]. Base on cancer biology and pharmacology progression, the modern scientific principle also can be adapted to TCM, such as herbs with apoptosis, autophagy or senescence inducing effects can be considered for anti-cancer therapy [32,33], herbs with anoikis inducing effects can be used for prevention of cancer metastasis [70].

## Future Directions

TCM can be used to alleviate symptoms, improve quality of life, prevent recurrence and metastasis, and prolong survival time. Scientifically combination conventional treatment with TCM may provide new insight into future practice of cancer medicine. However, as an ancient ethnomedicine, TCM must further develop effective herbal combinations or formulas for various situations in cancer treatment, elucidate herb effect mechanisms, understand combination

rule of anti-cancer herbs and herb-drug interaction, identify active herbal ingredients, and demonstrate clinical efficacy by high level randomized control trials.

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