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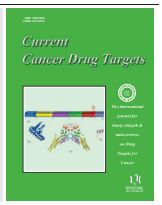
Advances in Synergistic Combinations of Chinese Herbal Medicine for the Treatment of Cancer



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Abstract: The complex pathology of cancer development requires correspondingly complex treatments. The traditional application of individual single-target drugs fails to sufficiently treat cancer with durable therapeutic effects and tolerable adverse events. Therefore, synergistic combinations of drugs represent a promising way to enhance efficacy, overcome toxicity and optimize safety. Chinese Herbal Medicines (CHMs) have long been used as such synergistic combinations. Therefore, we summarized the synergistic combinations of CHMs used in the treatment of cancer and their roles in chemotherapy in terms of enhancing efficacy, reducing side effects, immune modulation, as well as abrogating drug resistance. Our conclusions support the development of further science-based holistic modalities for cancer care.

Keywords: Cancer treatment, Chinese medicine, drug resistance, effect, immunity, side effects, synergistic combination.

INTRODUCTION

GLOBOCAN worldwide estimations indicate approximately 14.1 million new cancer diagnoses and 8.2 million cancer deaths in 2012. Furthermore, increased aging of the global population increases cancer risk, which makes cancer research more urgent than ever [1]. Cancer, which is a disease that is refractory to most current therapies, evolves progressively in an increasingly complex fashion, which is coordinated by multiple genes, proteins and their respective signal transduction pathways. Many factors work together to promote carcinogenesis and to enable initial tumor cells to acquire hallmark characteristics, including sustained proliferative signaling, replicative immortality, tumor-promoting inflammation microenvironmental modulation, invasive and metastastic capabilities, angiogenesis, abnormal cellular energetics and the ability to avoid anti-tumorigenic mechanisms including growth suppressors, immune destruction and cell death [2].

The complexity of cancer formation and development impairs effective treatment. Current treatments for cancer include surgery, radiotherapy, chemotherapy, targeted therapy, biotherapy as well as complementary and alternative medicine (CAM) therapies such as Traditional Chinese medicine (TCM). However, none of these modalities achieves optimal curative effects without adverse events. The traditional applications of individual single-target drugs are insufficient to treat complex diseases including cancer, cardiovascular diseases or Alzheimer's disease. Investigation of new anti-cancer treatment modalities is ongoing, and novel, more tolerable synergistic drug combinations (the simultaneous application of two or more drugs that interact to enhance therapeutic effects, reduce side effects, abrogate drug resistance and to modulate anti-tumor immunity) are emerging.

Principles of drug combinations might include the following: (1) drugs working on the same target *via* different pathways; (2) drugs working on different targets *via* the same pathway; (3) drugs working on different targets *via* different pathways; (4) drugs working on biological networks, involving complicated interactions among multiple genes, proteins and pathways at the pharmacological and pharmacokinetic levels. Notably, network analyses of drug combinations are just beginning, as the drug-gene-protein-pathway interaction databases are still far from being completely established.

Traditional Chinese Medicine, which is based on systematic theories, exhibits several favorable advantages by synergistically balancing natural medicinal herbs to match disease complexity. TCM considers the body as a singular complex system for treatment with Chinese herbal medicines (CHMs) and Chinese herbal formulae (CHFs) under the guidance of TCM theory. Each CHM is a mixture of multiple compounds. Many CHMs are bioactive, whereas individual isolated substituents might not exhibit bioactivity, indicating that multiple components within an herb work synergistically [3, 4]. Furthermore, formulae are more often applied in TCM. A formula generally is comprised of more multiple herbs, which are systematically arranged by a hierarchy ranking. Thus, the synergistic combinations of CHMs alone or in combination with chemotherapeutic drugs might be more applicable for the treatment of complex pathologies such as cancer. Holistic concept and syndrome differentiation in TCM theory are mainly explained in the

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view of philosophy. Nowadays, modern technologies have been applied to interpret them in a reductive way. To explore the complex mechanisms of synergistic combinations and seek for material basis for synthesized action of TCM treatment, experimental studies *in vitro* and *in vivo* were firstly undertaken. Much work has been devoted and more efforts are in need.

Complex interactions among herbs or their compounds require appropriate research approaches. Extensive efforts continue to be devoted to the development of efficient treatment methods, particularly for research of combinations of CHMs. Here, we list the most commonly used experimental designs and analytical methods for investigating combinations of CHMs (Table **1**).

SYNERGISTIC EFFECTS OF CHM COMPOUNDS, CHMS COMBINATIONS AND CHFS IN CANCER TREATMENTS

As previously mentioned, cancer cells can acquire ten "hallmarks" as originally proposed by Douglas Hanahan and Robert A. Weinberg [2]. Literature to date indicates that synergistic combinations of CHMs can downregulate proliferative signaling, inhibit tumor angiogenesis, promote cell death and inhibit invasion and metastasis. Normal tissues are capable of switching precisely regulating both growth-promoting and apoptosis-inducing signals to maintain cellular population. Thus, restoring normal proliferative activity represents one approach at treating cancer. Cell death, in the form of apoptosis, autophagy and necrosis, counteracts cellular overgrowth. Cancer cells can effectively escape such processes and exhibited unrestrained proliferation. Studies have demonstrated that autophagy can bi-directionally promote cellular survival and death [27]. Necrosis is not necessarily beneficial, as necrotic cells can release bioactive factors to induce the proliferation of neighboring cells, and can furthermore, attract inflammatory cells to consume or remove necrotic debris, which can facilitate tumorigenesis [28, 29]. As the roles of autophagy and necrosis are controversial in cancer, anti-cancer drug investigations have predominantly focused on apoptotic mechanisms. Angiogenesis represents another trait of cancer cells, as tumors require sufficient vasculature to acquire nutrients and to eliminate waste. Invasion and metastasis represents another basic trait of cancer cells as they progress to malignancy. This process affects both cellular morphology as well as reduces adhesion to stromal cells and to the extracellular matrix (ECM). Based on those hallmarks, synergistic combinations of CHM compounds and CHMs and CHFs were performed.

Synergistic Combinations of CHM Compounds

CHM compounds are bioactive, and studies of synergistic combinations of CHM compounds for the treatment of cancer have predominantly focused on curcumin, quercetin and resveratrol-based combinations.

Curcumin is the main active component of turmeric (Curcuma longa L.), which is a member of the ginger (Zingiberaceae) family. Curcumin has been reported to exhibit anti-inflammatory, antioxidant and chemotherapeutic effects and does not elicit toxicity in laboratory animals even at high doses [30, 31]. Curcumin acts on the expression of tumor suppressor genes, apoptotic genes, oncogenes, and their respective proteins and signal pathways [32]. Several CHM compounds have been combined with curcumin to enhance treatment efficacies. *In vitro* and *in vivo* studies have shown that curcumin and resveratrol combinations can enhance apoptotic effects in the head and neck carcinomas cells, including upregulation of PARP-1 cleavage and Bax/Bcl-2 ratio and downregulation of ERK1 and ERK2 phosphorylation. Those effects were elicited more significantly by the combination treatments than that by treatment with the application of curcumin alone [33]. Curcumin has also been combined with triptolide to promote apoptosis in ovarian cancer cells, accompanied by HSP27 and HSP70 down regulation [34]. In addition, the combination of curcumin and emodin was reported to decrease the proliferative and migratory ability of breast cancer cells [35]. Different combinations of CHM compounds with curcumin have achieved similar and different biological effects in cancers, as detailed in Table **2**.

Resveratrol exhibits a range of beneficial activity, including chemoprevention and anti-tumor effects [36].

Table 1. Designs and analysis methods for CHMs combination.

CHM Combinations	Experimental Designs	Analysis Methods and Models	Refs.
Herbal pairs	uniform design, fixed ratio design	F-test, high-dimensional B-splines, loewe additivity, bliss independence, nonlinear mixed-effects modeling, combination index method and isobologram techniques, Combo method, target inhibition networks, curve-shift analysis, surface of synergistic interaction analysis, separate ray model, pharmacokinetic-pharmacodynamic model and additive damage model	[5-13]
Multiple drugs	factorial design，uniform design	semi-parametric response surface model, response surface model, combination index method, isobologram techniques, standard FIC index model, target inhibition networks, formal model, network topology analysis, drug Combo Ranker, emax model and bivariate thin plate splines.	[6, 9, 14-22]
Formula	Uniform design, orthogonal design	systems-pharmacological and distance-based mutual information models, chemometric techniques, prediction pharmacodynamics model.	[23-26]

Table 2. Synergistic combinations of CHM compounds.

CHM Compound 1	CHM Compound 2	Effects	Mechanisms	Cancers	Refs.
Curcumin	resveratrol	↑apoptosis; ↓proliferation	↑antioxidant enzymes, PARP-1 cleavage, Bax/Bcl-2 ratio, p53 activation; ↓enzyme activities of drug-metabolizing enzymes, ERK1 and ERK2 phosphorylation, LC3 II, XIAP and survivin expression, NF-kappaB activity, p-Akt, cyclin D1	lung cancer, head and neck carcinoma, hepatocellular carcinoma, breast cancer, colon cancer, prostate cancer, neuroblastoma.	[33, 51-55]
	triptolide	↑ apoptosis	↑ HSP27 and HSP70	ovarian cancer	[34]
	emodin	↓ proliferation, invasion	↑ miR-34a ; ↓TGF-β signaling pathway	breast cancer, cervical cancer	[35, 56]
	arctigenin+green tea polyphenol	↓ proliferation, migration	↑ Bax/Bcl-2 ratio; ↓ NF kappaB, PI3K/Akt and Stat3 pathways	prostate cancer, breast cancer	[57]
Quercetin	arctigenin	↓proliferative, migration	↓AR and PI3K/Akt pathways and oncogenic microRNAs	prostate cancer	[42]
	hyperoside	↑ programmed cell death; ↓ metastasis, proliferation, angiogenesis.	↓ miR21 signaling pathway, oncogenic microRNA-27a	prostate cancer, leukemia cells, renal cancer	[43, 44]
	1,2,3,4,6-penta-O-galloyl-beta-D-glucose (5GG)	↑ S-phase arrest, G2/M-phase arrest and apoptosis	↓ S-phase kinase protein 2 and Her2 expression	breast cancer	[58]
	resveratrol	↓ proliferation survival and angiogenesis	↓ oncogenic microRNA-27a,phosphorylation of Akt	colon cancer, glioma	[45, 59]
	EGCG/green tea polyphenols	↓ proliferation	↑ bioavailability, intracellular concentration of EGCG; ↓ methylation of green tea polyphenols	prostate cancer	[60, 61]
Paclitaxel	curcumin	↑apoptosis; ↓proliferation, drug resistance	↓EGFR signaling, NF-κB activity, glycogen synthase kinase-3	breast cancer, hepatocarcinoma, cervical cancer, ovarian cancer, brain tumor	[62-66]
Taxifolin	andrographolide	↑mitotic arrest and apoptosis	disrupting microtubule dynamics and activating the spindle assembly checkpoint	prostate cancer	[67]
Resveratrol	matrine	↑apoptosis; ↓proliferation	↑caspase-3 and caspase-9; ↓survivin	hepatoma	[39]
	arsenic trioxide	↑ apoptosis, angiogenesis	↑ poly (ADP-ribose) polymerase, (PARP) and its cleaved isoform	ovarian cancer, breast cancer, acute or chronic myeloid leukemia cells, lung adenocarcinoma	[40, 68, 69]
	genistein	↑ apoptosis; ↓drug resistance	↑ caspase cascade; ↓ expression of HDM2. MRP2	ovarian cancer, cervical cancer, liver cancer, prostate cancer	[41, 70, 71]
Artesunate	triptolid	↑apoptosis	↑HSP 20 and HSP 27	pancreatic cancer	[72]
	allicin	↑apoptotic rate; ↓viability, invasion, motility and colony formation ability	↑caspase-3/9	osteosarcoma	[73]
Arsenic trioxide	berberine	↑apoptosis cell; ↓viability	↑caspase-3; ↓Bcl-2, Bid, Bcl-x/L, PKC-mediated signaling pathway	neuroblastoma, glioma	[74, 75]
	salvianolic acid B	↑apoptosis	↓Bcl-2, p-Akt	hepatoma and breast cancer	[76]

↑: Up-regulation
↓: Down-regulation

Synergistically combining resveratrol and tanshinone IIA at a ratio of 1:1 or 1:2 induced cisplatin-comparable cytotoxicity in hepatocellular carcinoma cells. The proportion of apoptosis (sub-G1 cell cycle accumulation) and DNA fragmentation were increased more significantly by the combination compared to single-agent treatments [37]. Resveratrol elicited more significant inhibitory effects on ovarian and hepatocellular carcinoma cells when combined with artemisinin at a ratio of 2:1 by increasing apoptosis, ROS levels and by decreasing migratory ability [38]. Combinations of resveratrol with matrine, genistein and arsenic trioxide have been used in the treatment of hepatoma, breast cancer and acute and chronic myeloid leukemias [39-41].

Quercetin is another commonly used CHM compound and is found in many fruits, vegetables and grains. Generally, quercetin has been applied in combined with arctigenin, hyperoside and resveratrol. These combinations have improved anti-cancer effects compared to the application of the individual agents by regulating proliferation, migration, angiogenesis and apoptosis processes in prostate cancer, leukemia, breast cancer and pancreatic cancer cell lines [42-45].

Both baicalin and baicalein are CHM compounds that are extracted from *Huangqin* (Scutellaria baicalensis), an herb that is commonly used to treat cardiovascular diseases, hypertension and cancer [46]. The combination of these two herbal compounds elicited more significant induction of apoptosis in human breast cancer cells compared with the application of either agent alone. Synergistic effects were achieved in terms of ERK / p38 MAPK activation, as well as activation of caspases-3, caspase-9, Bcl-2, Bax and p53 [47]. *Zuojinwan* has been reported to inhibit the growth of hepatocellular carcinoma [48]. Further studies have shown that the active components of *Zuojinwan*, berberine and evodiamine, can synergistically promote cancer cell apoptosis *in vitro* [49]. A docking analysis has shown that panaxadiol and epigallocatechin gallate can synergistically impair the proliferation of human colorectal cancer cells, as these two compounds bind to two different sites of the annexin V protein [50]. Other CHM combinations, including taxifolin with andrographolide, triptolid with artesunate, artesunate with allicin, evodiamine with norcantharidin, or berberine with arsenic trioxide are listed in Table **2**. Most CHM compound combinations are currently in the experimental stage of pre-clinical studies. Further investigation is warranted to clearly understand the crosstalk between CHM compounds.

As shown in Table **2**, actions of curcumin-based combinations were tested on different cell lines, especially on prostate and breast cancers and studies has shown apparent efficacy *via* different mechanisms. Among them, combinatorial use of curcumin and resveratrol was most widely studied in diverse cancers. Queretin-based combinations were mainly explored on prostate cancer and has significantly enhanced the therapeutic effect. Additionally, resveratrol-based combinations in different experiments demonstrated good effects on ovarian cancer cells. To seek for the best CHM combinations for certain kind of cancers and determine the tissue context dependence, more studies on diverse cancers should be taken.

Synergistic Effects of CHMs Combinations

CHMs combinations represent the core of CHFs. TCM physicians combine CHMs to enhance therapeutic effects and alleviate toxicity and side effects.

Yanhusuo (Rhizoma corydalis) extract has been reported to weaken the invasiveness and metastatic capacity of breast cancer cells. Furanodiene, which is isolated from *Ezhu* (Rhizoma curcumae), has been reported to elicit anti-proliferative effects and apoptosis in lung cancer cells [77, 78]. Further investigation of the synergistic effects of *Ezhu* and *Yanhusuo* indicated that combination treatments of *Ezhu* and *Yanhusuo* at a ratio of 3:2 could reduce the proliferative and invasive capacities of breast cancer cells more significantly and induce more cytochrome c release (which initiates apoptosis) than the individual treatment with either *Ezhu* or *Yanhusuo*. Furthermore, one of the synergistic mechanisms regulating p-ERK level was reduced [79].

Another study demonstrated that the actions of *Juhua* (Dendranthema morifolium) and *Donglingcao* (Rabdosia rubescens) are additive, as are those of *Huangqin* (Scutellaria baicalensis) and *Juhua*, suggesting that the combination of these herbs work on similar molecular targets or metabolic pathways. However, combinations of *Huangqin* and *Gancao* (Guralensis), *Huangqin* and *Donglingcao*, *Gancao* and *Donglingcao*, *Gancao* and *Juhua* have been reported to exhibit antagonistic effects on the viability of prostate cancer cell lines *in vitro*, whereas the combination of all four herbal extracts inhibited cancer cell growth more significantly compared to their individual application alone. However, further investigations on the underlying mechanisms are needed [80].

Cili (Rosa roxburghii tratt) and *Jinqiaomai* (Fagopyrum cymosum) have been combined to suppress proliferation and promote apoptosis of esophageal squamous carcinoma, gastric carcinoma and pulmonary carcinoma cells *in vitro*, predominantly by increasing Bax levels and reducing Bcl-2 expression [81]. Another study showed that *Lingzhi* (Ganoderma lucidum) potentiated the cytotoxic effects of *Yunzhi* (Coriolus versicolor) on leukemia cells. Treatment with this combination also resulted in reduced Rb phosphorylation and increased poly (ADP−ribose) polymerase (PARP) cleavage [82].

Synergistic Effects of CHFs

CHFs are composed of several CHMs, each of which plays a different role (*e.g*., monarch, minister, assistant or guide according to CHF-construction principles in TCM). The effects of each ingredient in CHF are not additive in an accumulative fashion but rather interact with each other intricately to enhance curative effects and reduce undesirable effects.

For example, the logically constructed formula *Fufang qingdai pill* (Realgar-Indigo naturalis formula) is commonly used to treat acute promyelocytic leukemia (APL). The formula consists of *Xionghuang* (Realgar), *Qingdai* (Indigo naturalis) and *Danshen* (Salvia miltiorrhiza), as directed by CHF construction principles. Three main active compounds, tetraarsenic tetrasulfide, indirubin and tanshinone IIA, were

derived from the formula. Among them, tetraarsenic tetrasulfide predominantly targeted the ubiquitination of the PML-RARα fusion protein, which is attributable for the development of APL. Neither indirubin nor tanshinone IIA affected the fusion protein but was able to enhance the activity of tetraarsenic tetrasulfide. Moreover, indirubin acted as a CDK inhibitor, blocking cell growth and potentiating the anti-tumor effects of tetraarsenic tetrasulfide. Those three compounds worked synergistically to treat APL, and their cooperative form is consistent with CHF construction principles [83].

Another classic formula, *Liuwei dihuang wan*, is comprised of *Shanzhuyu* (Fructus corni), *Zexie* (Rhizoma alismatis), *Danpi* (Cortex moutan), *Dihuang* (Radix rehmaniae), *Fuling* (Poria cocos) and *Shanyao* (Rhizoma dioscoreae). A manual literature analysis highlighted the target genes of each herbal component; in total, formula affected 146 genes. Among them, 127 genes represent nodes for protein-protein interaction network. Further analysis indicated that those genes might serve as the potential targets for the treatment of 9 types of cancer, 5 types of neurological, endocrine, immune, or metabolic system disorders as well as 2 types of cardiovascular diseases. A newly established distance-based mutual information model (DMIM) database expanded the *Liuwei dihuang wan*-targeted genes from 146 to 224, and the number of network nodes increased to include 173 genes. Although DMIM requires further improvement, it illustrates the complex network effects of CHFs. Richer databases and enhanced model are urgently needed to determine the compatibility mechanisms of CHMs combinations or CHFs [24].

Significant crosstalk among active compounds in each CHM and their combinations in CHF has brought more difficulties for researchers. Most investigations have been preliminary and it is also necessary to seek for efficient approaches on CHF researches.

SYNERGISTIC EFFECTS AND UNDERLYING MECHANISMS OF CHM COMPOUNDS, CHM OR CHFS RESPECTIVELY COMBINED WITH CHEMO-THERAPEUTIC DRUGS IN THE TREATMENT OF CANCER IN CLINICAL

The combinatorial use of CHM compounds, CHM or CHFs with chemotherapeutics has yielded encouraging results. The proper addition of CHM compounds, CHMs or CHFs enhances immunity and improves tolerance to chemotherapy, potentiates the cytotoxicity induced by chemotherapeutic drugs, and largely alleviates their side effects, ultimately improving patient quality of life and prolonging lifespan.

Previous research has demonstrated that competent immune systems can significantly reduce tumor incidence and development, resulting in improved prognosis [84]. Thus, the improvement of immunity represents a therapeutic approach to impair and even arrest tumor progression. In a clinical trial on 105 patients, a mixture of citronella isolated from *Tianzhukui* (Geranium) and extracts from *Lingzhi* (Ganoderma lucidum), *Dangshen* (Codonopsis pilosula) and *Danggui* (Angelicae sinensis) could apparently reduce the leukocyte depletion for cancer patients undergoing chemotherapy or radiotherapy. The mixture modulated the immunity to help the body fight against cancer cells [85]. A double-blind placebo-controlled randomized trial on patients with ovarian cancer showed that additive use of TCM to conventional chemotherapy indeed had less decreased lymphocytes counts, which helped to keep patients' tolerance to further therapy [86].

CHM compounds, CHMs or CHFs might significantly enhance the cytotoxic effects of chemotherapeutic drugs. A prospective, phase II study on patients with elapsed or refractory multiple myeloma showed that the efficacy of melphalan was improved when treated in combination with ascorbic acid and arsenic trioxide [87]. Combinatorial use of trumeric powder and imatinib decreased the nitric oxide (NO) levels in chronic myeloid leukemia more obviously than imatinib used alone and the NO has been found to be associated with angiogenesis [88, 89]. The combination of *Shengmai injection* and *Gujin granule* were reported to potentiate the short-term cytotoxicity induced by navelbine and cisplatin chemotherapy for patients with advanced non-small cell lung cancer and their median survival time was also prolonged [90]. Another CHF injection, *Shenqi fuzheng injection* has also been reported to be effective against non-small cell lung cancer. A meta-analysis covering 2062 patients demonstrated that the efficiency of platinum-based chemotherapy was enhanced by intravenous dripping of *Shenqi fuzheng injection* [91]. A another randomized and controlled clinical trial evidenced that the injection also increased the curative effects of cyclophosphamide, epirubicin and 5-fluorouracil regime, accompanied with the growth of T-lymphocyte subgroup and NK cells for local advanced breast cancer patients [92]. A systematic review demonstrated that astragalus-based Chinese herbs enhanced the inhibitory effects of platinum-based chemotherapy in advanced non-small-cell lung cancer [93].

Conversely, adverse events, including nausea, vomiting, and anorexia, often accompany chemotherapy. Therefore, relieving side effects represents a significant rationale for the application of CHMs during chemotherapy. The additive use of astragalus polysaccharide significantly alleviated side effects including fatigue, nausea and vomiting, pain and loss of appetite associated with treatment with vinorelbine and cisplatin in patients with advanced NSCLC, greatly improving their quality of life [94]. A phase II study showed that *Huangqi* (Astragali radix)-based decoction relieved the cancer-related anorexia [95]. PHY906 consists of *Gancao* (Glycyrrhiza uralensis Fisch), *Shaoyao* (Paeonia lactiflora Pall), *Huangqin* (Scutellaria baicalensis Georgi) and *Dazao* (Ziziphus jujuba Mill) and has long been used for a variety of maladies. The formula decreased the incidence of side effects elicited by irinotecan, 5-fluorouracil or leucovorin in colon carcinoma patients and capecitabine in hepatocellular carcinoma patients [96, 97]. Injections of Chinese herbs or CHFs have been applied as a clinical cancer therapeutic. A network meta-analysis demonstrated that the FOLFOX regimen, when combined with injection of *Kanglaite*, Astragalus polysaccharides and *Yadan ziyouru,* generally enhanced the quality life of gastric cancer patients, and reduced side effects including leukopenia [98]. *Aidi injection* also attenuated the side effects elicited by FOLFOX4 for patients with advanced colorectal cancer [99]. Quercetin and

resveratrol were found to alleviate the cardiotoxicity inducted by doxorubicin [100]. The additive use of TCM to chemotherapy was able to protect the liver, resulting in lower serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels than chemotherapy used alone [101]. Mistletoe extract and arsenic trioxide were applied more in clinical to reduce the adverse effects caused by chemotherapy (Table **3**).

To explore the cellular mechanisms under those combinations, great amount of studies on cancer cell lines were undertaken and the modes of CHMs interacting with chemotherapeutic drugs were summarized as follows: (1) inhibit cancer cell growth and reduce dosages of chemotherapeutic drugs to achieve equivalent or enhanced curative effects, consequently reducing drug-induced adverse events; (2) create new inhibitory effects when combined with chemotherapy drugs; (3) improve the patient immunity enhance tolerance for further chemotherapy; (4) act as chemotherapeutic drug sensitizer; (5) help the absorption of drugs to enhance the drug effects (for example, curcuma increased the absorption of rhizoma paridis spooning to enhance anti-tumor effects [102]. Notably, individual herbs or CHM compounds might participate *via* several modes. For example, ursolic acid enhances the curative effects of capecitabine by downregulating multiple tumor-related inflammation, proliferation, invasion, angiogenesis and metastasis mechanisms [103].

Currently, most of researches are still in the experimental stage and quite limited clinical trials are available to precisely evaluate CHM compounds, CHMs or CHFs' contribution to conventional chemotherapy. Presently CHMs and CHFs are rarely used alone in the treatment of cancer in clinical and mainly act as a supplementary and adjunctive strategy due to their insignificant or unconfirmed antitumoral efficacy. Even when used in combination with conventional chemotherapy occasionally, a limited efficacy has been

Table 3. Synergistic combinations of CHM compounds or CHMs with chemotherapeutic drugs in clinical.

CHM Compounds/CHMs	Chemotherapeutic Drugs	Designs	Case Numbers	Cancers	Clinical Outcomes	Refs.
Arsenic trioxide	ascorbic acid+melphalan	prospective, multicentre, single-arm	65	multiple myeloma	↑ therapeutic effect and tolerance	[104]
	all-trans retinoic acid	randomized, controlled	61	acute promyelocytic leukemia	↑ quality of complete remission, the status of the disease-free survival	[105]
	dexamethasone+ascorbic acid	a phase 2 trial.	20	multiple myeloma	↑tolerance;↓ adverse events	[106]
Mistletoe extract	cyclophosphamide + adriamycin +cisplatin /cyclophosphamide +adriamycin +5-fluorouracil	Prospective, Randomized, Controlled	68	breast cancer	↑quality of life;↓reduce the side-effects	[107]
	cyclophosphamide +cisplatin/ifosfamide +carboplatin	A Prospective Randomized Controlled Clinical Trial	71	ovarian cancer	↑ quality of life;↓reduce the side-effects	[107]
	vinorelbine +cisplatin /mitomycine+vindesine +cisplatin	A Prospective Randomized Controlled Clinical Trial	94	non-small cell lung cancer	↑ quality of life;↓reduce the side-effects	[107]
	cyclophosphamide+methotrexate+fluorouracil	randomised, placebo-controlled, double-blind, multicentre	272	breast cancer	↑ quality of life	[108]
	cisplatin+5-fluorouracil/5-fluorouracil	randomized, controlled	20	ear, nose and throat carcinoma	↑ immunological reactions, microcirculation	[109]
Turmeric powder	imatinib	randomized, controlled	50	chronic myeloid leukemia	↑ therapuetic effect	[88]
Astragalus polysaccharide injection	vinorelbine and cisplatin	randomized, controlled	136	non-small cell lung cancer	↑ therapeutic effect, quality of life ; ↓reduce the side-effects	[110]
Cimicifuga racemosa	tamoxifen	prospective	50	breast cancer	↓ psychovegetative symptoms	[111]
Scutellaria baicalensis	irinotecan	randomized, controlled	44	non-small cell lung cancer	↓ gastrointestinal toxicity	[112]

↑: Up-regulation
↓: Down-regulation

Table 4. Combinations of CHM compounds/CHMs/CHF with chemotherapeutic drugs that elicited have adverse events.

CHMs Compounds CHMs/CHFs	Chemotherapeutic Drugs	Cancers	Adverse Events	Study Types	Refs.
Songrong (Agaricus blazei)	cisplatin+cyclophosphamide	ovarian cancer	hepatotoxicity	case report	[117]
Renshen (ginseng)+selenium	gefitinib	lung adenocarcinoma	disease progression speeding	case report	[118]
Injections of Nerium oleander	ifosfamide+etoposide	knee synovial carcinoma	hepatotoxicity, cardiopulmonary arrest	case report	[119]
Amygdalin+vitamin C	cisplatin+gemcitabine	bladder urothelial carcinoma	tachycardia, tonic–clonic seizures	case report	[120]
Xanthorrhizol	tamoxifen	breast cancer	promte tumor growing	experimental study	[121]

reported generally and only few of them (in particular astragalus, arsenic trioxide or mistletoe-based Chinese herbs) seem to be beneficial in some way. What's more, some reports has evidenced the severe risk of Chinese herb-drug interactions (Table **4**). Therefore, more reliable studies and methods should to applied to evaluate the actions of CHM-related combinations on cancer treatment prudently and objectively.

UNWANTED SIDE EFFECTS OF SYNERGISTIC COMBINATIONS

Actually, the concomitant use of CHM compounds, CHMs or CHFs with or without chemotherapy might fail to achieve synergistic efficacy; for example, *kanglaite* didn't bring about additional benefits to patients with advanced breast cancer receiving mitomycin-C or cisplatin [113]. What's worse, not all combinations are free from harm. Some combinations may interfere with the metabolism of concurrently used drugs, consequently compromising the chemotherapy's efficacy, even increasing risks of hepatotoxicity, nervous system damage, or reduced curative effects (*e.g*., *via* herb-drug interaction) [114]. *Siwutang* reversed the anti-proliferative effects of tamoxifen and increased levels of estrogen receptor alpha and N-cadherin. However, this formula was also reported to attenuate the anti-proliferative activity of trastuzumab by increasing the phosphorylation of the cell cycle regulatory protein p27 (Kip1) [115]. A combination of *Baihuasheshecao* and *Dihuang* was reported to inhibit the expression of CYP3A4, another drug antiporter, consequently increasing the potential toxicity of drugs and narrowing the therapeutic window [116]. More examples were listed in Table **4**. As the CHM-CHM or CHM-drug interaction is complicated and the mechanisms largely remain obscure. In addition to the desired curative effects, potential unintended side effects deserve equal attention.

PERSPECTIVES AND CONCLUSIONS

The complex biology of cancer development requires relatively complex treatment approaches. Cancer development involves multiple genes, proteins and pathways, as well as intricate crosstalk among them. Thus, the application of synergistic combinations of drugs has emerged as a therapeutic approach and continues to play an important role in the treatment of cancer, particularly in terms of combination of CHMs, which are unique in their formulae and applications. The application of synergistic combinations of CHMs for the treatment of cancer has produced intended therapeutic effects, particularly when combined with chemotherapy, in terms of enhancement of curative effects, reduction of adverse events associated with conventional therapies, improvement of patient immunity, eventually promoting patient rehabilitation, improving quality of life and prolonging their lifespan.

Enhanced therapeutic efficacy produced by combinations of CHM compounds, CHMs and CHFs were generally achieved *via* inducing apoptosis, reducing proliferation, migration and angiogenesis, as well as altering cell cycle dynamics and cell viability by regulating relevant gene expression and protein signaling pathways in many kinds of cancer cell lines according to pre-clinical researches. However, in clinical their efficacy was compromised. There is a big discrepancy between experimental data and clinical use. Main reasons may includes: (1) the human body works intricately and the cancer complicates the complexity; (2) CHMs or CHFs contains many ingredients and there are inherently complex interactions among those ingredients in a single herb or formula, especially when they entered into the body; (3) the microenvironment of cancer cells in the body might also affect cells' response to herbs or drugs. But such microenvironment is hard to imitate *in vitro*; (4) cancer cells in the body develops gradually and continuously; however, cells lines *in vitro* are in a relatively stable condition. Therefore, experimental and clinical results might not be consistent; (5) some studies either in pre-clinical or clinical are of low quality; (6) in China, only being approved as new drugs, can these CHM compounds be studied in clinical legally. To overcome those limitations, firstly, more efficient and reliable methods for researching as well as estimating the synergistic effects of CHMs-related combinations should be optimized, like the network-based approach, pharmacological networks [122]. Secondly, studies of high quality, especially in clinical are needed. Thirdly, apart from exploring the association of certain genes, proteins or pathways with synergistic combinations, explaining the roles of tumor-promoting inflammatory microenvironment and abnormal energy metabolism and how they are interfered by herb-herb or herb-drug combinations should be emphasized. Additionally, mechanisms of CHMs and CHFs action needs to be revealed to find a critical point that correlates cancer initiation or progression processes to herbs or drugs' targets.

Unveiling the tissue context dependence of CHMs-related combinations is also on the agenda. So a far way lies ahead to bridge the gap between experimental data and clinical application.

CONFLICT OF INTEREST

All authors confirm that this article content has no conflict of interest.

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