THOMSON REUTERS

Current Opinion in Drug Discovery & Development 2010 **13**(1):50-65
 ISSN 2040-3437

REVIEW

Interactions between traditional Chinese medicines and Western therapeutics

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Traditional Chinese medicine (TCM) is a holistic approach to health that attempts to bring the body, mind and spirit into harmony. TCM is an essential part of the healthcare system in several Asian countries, and is considered a complementary or alternative medical system in most Western countries. An integration of the traditional Chinese and Western systems of medicine has begun in multiple medical centers internationally, and there is increasing evidence that several herbs and combinations of herbs used in TCM impart important pharmacological effects. The number of databases and compilations of herbs, herbal formulations, phytochemical constituents and molecular targets is increasing, primarily because of the widespread use of TCM in combination with Western drugs. The continued popularity of herbal remedies worldwide suggests that evidence-based research in this field, as well as information regarding the potential efficacy and safety of phytochemical constituents in herbs and TCM formulations, are essential, particularly when TCM is used in combination with other drugs. Herb-drug interactions are similar to drug-drug interactions in terms of their effects on ADME properties. Improvements in the knowledge of the molecular targets and metabolic pathways, as well as of the synergistic and inhibitory effects associated with important phytochemicals from herbs and herbal formulations, will lead to the development of rational approaches for the safe combination of healthcare systems from different cultures.

Keywords GeneGo, herb-drug interaction, MetaDrug, phytochemical, quantitative structure-activity relationship, TCM, traditional Chinese medicine

Abbreviations

BPCD Bioactive Plant Compounds Database, **CAM** complementary and alternative medicine, **CHCD** Chinese Herbal Constituents Database, **CHMIS-C** Comprehensive Herbal Medicine Information System for Cancer, **TCM-ID** Traditional Chinese Medicine Information Database, **WCA** Wei Chang An formulation

Introduction

Herbal remedies, particularly those used for medicinal or therapeutic purposes, are widely used throughout the world. Traditional medicine, which incorporates the therapeutic use of herbs and other natural products, has been embedded in many cultures for thousands of years. In most developing countries, including China, there is an extensive foundation for the therapeutic effects of herbal medicines that is derived from the established use of such agents in combination with supportive research data, including clinical trial results. The WHO has estimated that approximately 80% of the global population relies on traditional herbal medicines as part of standard healthcare [1] and, in the US, where herbal remedies are classified as dietary supplements, an estimated 1 in 5 adults regularly consumes herbal products [2]. In July 2009, the National Center for Complementary Medicine, which is part of the NIH, reported US $14.8 billion out-of-pocket spending per year in the US on non-vitamin, non-mineral natural products; this amount is approximately one-third of the total spending on pharmaceutical products [3].

The need for additional evidence-based research into the efficacy and safety of phytochemical constituents in herbs and in traditional Chinese medicine (TCM) formulations is of particular importance, as the concept of integrated medicine (ie, the combination of traditional and conventional, or Western, medicine) is becoming more widely used. The concept of integrated medicine originated in China; the Chinese Association of Integrated Chinese and Western Medicine Research was established in Beijing in 1981, and was subsequently renamed the Chinese Association of Integrated Medicine (CAIM) in 1990. The CAIM led the expansion of integrated medicine, and more than ten universities in China specialized in this research area at the time of publication. The overall focus of the CAIM has been on the development of novel approaches for the

treatment of diseases, including cancer, cardiovascular disease, dementia, diabetes, drug addiction, HIV/AIDS, multi-organ failure, osteoporosis and viral hepatitis [4]. China's medical universities emphasize that TCM should complement modern Western medical treatments, and curricula are designed to feature both modalities, thereby allowing trained practitioners to prescribe both Chinese and Western medicines. Thus, healthcare providers using integrated medicine focus on four key components: (i) the values and philosophy behind the treatment; (ii) the treatment design (ie, the modality and mechanism of action); (iii) the treatment process itself; and (iv) the outcomes of the treatment [4]. Acknowledging China's multitude of lower- and middle-class citizens, practitioners are also aiming to make integrated medicine an affordable and accessible treatment option.

The NIH has defined Complementary and Alternative Medicine (CAM) as a 'group of diverse medical and healthcare systems, practices and products that are not generally considered to be part of conventional medicine'. While alternative medicine is used instead of conventional medicine, complementary medicine is used in conjunction with conventional therapeutics. According to the NIH, integrated medicine encompasses the use of both conventional and alternative therapies for which there is 'evidence of safety and effectiveness' [5]. In 2005, the Institute of Medicine of the National Academies released a report recommending that medical schools include sufficient information in their standard curricula to enable licensed professionals to offer advice to patients regarding CAM competently [6]. In 1990, an estimated one-third of the US population used at least 1 out of 16 specified alternative therapies [7]. In 2002, more than one-third of US citizens were estimated to have used CAM within the previous 12 months, and more than one-half of patients aged 18 years or older used CAM therapies in addition to conventional therapies because of the belief that CAM treatments increased the beneficial effects of conventional drugs [8,9]. As the popularity of CAM has increased, healthcare institutions have started to integrate CAM therapies into established treatment programs. Examples of institutions that have developed integrative medicine programs include the University of California, San Francisco (UCSF) Osher Center for Integrative Medicine [10] and the University of California, Los Angeles (UCLA) Collaborative Centers for Integrative Medicine [11]. Both of these centers seek to improve the understanding of practitioners of cross-cultural and interdisciplinary healthcare in order to optimize patient care.

The combination of TCM and conventional therapies creates a need for an improved understanding of the benefits and risks associated with using different forms of treatment concurrently, particularly regarding herb-drug interactions, by both physicians and patients. As patients often receive more than one type of treatment, and less than 40% of complementary or alternative therapies are disclosed to physicians by patients, the side effects and outcomes of the application of combined therapies are difficult to predict. In many cases, adverse interactions between herbs and conventional treatments remain unknown or unrealized [4,8].

This review highlights the known interactions, both synergistic and antagonistic, between certain herbs and phytochemical constituents and Western therapeutics, and discusses novel methods for deconvoluting protein targets and drug-phytochemical interactions. Unless otherwise specified, herbs discussed in this review are represented as follows: *common Chinese name* (*botanical name*; Chinese pharmaceutical name).

History and principles of TCM

The holistic TCM approach toward achieving harmony includes acupuncture, dietary therapies, Tui na and Shiatsu massage, in addition to the herbal medicines that are the focus of this review. The principles of TCM are centered on the theory that harmony between two opposite forces, *Yin* and *Yang,* is the crux of health, whereas disease results from disharmony between these forces [12]. Imbalance can be caused by an array of external forces, and TCM practitioners advise patients to replenish *Yin* or *Yang* when deemed appropriate [13]. In TCM theory, medicinal herbs are based on various patterns of body deficiency: *Yin*-nourishing, blood-enriching, *Yang*-invigorating and Qi-invigorating [14,15]. In comparison to Western medicine, *Yin*- and *Yang*-based harmony is similar to the homeostatic state. Ko *et al* also linked *Yang*–invigorating herbs with a tendency to increase wellbeing, potentially through enhancing mitochondrial oxidative processes [14], and Zhu and Woerdenbag linked *Yin*–nourishing herbs with maintaining mitochondrial ATP generation [15].

Although many substances used in TCM are classified under the collective term 'herbal medicine', several of these therapeutics are derived from animals or minerals rather than plants [15]. All of these substances are described in TCM practice based on several characteristics, including taste, ethnobotanical classifiers or characteristics, meridian tropism, compatibility, contraindication, toxicity and preparation of the given herb concoction. The link between the taste and the therapeutic characteristics of various substances used in TCM is somewhat obscure; however, Liao *et al* reported a correlation between traditional TCM flavors and the antioxidant activity of 45 herbs used in several cardiovascular TCM herbal formulations [16]. TCM herbal formulations are based on the concept of combining different compounds to increase or promote therapeutic effectiveness, minimize toxicity and side effects, accommodate the promotion of harmony, and optimize the therapeutic effects of each component [15,17,18]. Synergism may also occur through the effects of phytochemicals in the concoction of herbs. An example of synergism is illustrated by individualized formulations for the treatment of hepatitis viral infection, in which several herbs are used, including *huang qi* (*Astragalus membranaceus*; Radix Astragali), *chi shao* (*Paeonia lactifora* and *Paeonia veitchii*; Paeoniae Radix rubra), and

hu zhang (*Polygonum cuspidatum*; Polygoni cuspidati Rhizoma). A synergistic antiviral effect between *huang qi* and *hu zhang* has been identified in Hep-2 cell assays and in a clinical trial in patients infected with HCV [19].

TCM anticancer formulations may also function on the principle of synergism. Although many TCM anticancer formulations have been reported to induce apoptosis in cancer cells, the mechanism of action of these formulations may also involve non-apoptotic anticancer activity [20]. For example, a common herb in anticancer TCM herbal concoctions is *huang qin* (*Scutellaria baicalensis*; Scutellariae Radix*)*, which is also known as 'Baikal skullcap roots' or 'Golden roots' [21,22]. The mechanism of action of *huang qin* involves the inhibition of eicosanoid synthesis, which mediates inflammation and tumor cell proliferation via COX-2 and lipoxygenase, respectively [22]. Several other TCM anticancer herbs are thought to reduce tumor growth and the development of cancer through anti-angiogenic effects [23], thereby circumventing multidrug resistance and strengthening the immune system [24,25].

Regulation and use of herbal medicines

The regulation of herbal medicines varies significantly between countries and regions of the world. Reviews by Foster *et al* [1] and Bent [2] discussed the range of classifications for the same preparations; in the US, TCM preparations are described as dietary supplements; in Canada and Australia, these preparations can be described as natural health products; and in Europe, traditional medicines are regulated as drugs under the European Scientific Cooperative on Phytochemistry. In August 2009, a UK-wide consultation intending to determine whether a regulatory system should be established to govern the practice of complementary and alternative therapies, including TCM, was announced [26]. The most stringent controls on the chemical quality of traditional medicines occur in Europe and Japan [1]. In Japan, approximately 150 traditional medicines (both Japanese and Chinese) have been approved and appear on the Japanese National Health Insurance Drug Tariff [27].

A continuing issue regarding controlling the quality of herbal medicines is the difficulty in establishing the correlative content and/or quality of the herb/herbal preparation/phytochemical assessed in individual herbal efficacy and toxicity studies [1], creating challenges in designing controlled clinical trials with reproducible results, as well as in standardizing the compounds and techniques used and in monitoring quality assurance [17]. The significant variations in the content and quality of the phytochemical constituents of herbal remedies can be attributed to genetic and environmental conditions, such as diversity within a plant species, redundant pharmacological activity within combinations of herbs, multiple phytochemical analogs within a plant, and seasonal and regional differences in herb growth [28-30]. In addition, variation in the preparation methods used for herbal concoctions, such as powdering and extracting with various solvents and brewing teas, can alter the percentage of constituents present in the final remedy. Several studies have identified dissolution differences when the particle sizes vary between raw material and powder formulations [31-33], and conditions such as temperature, concentration, agitation and the total time for which teas or other infusions are brewed/extracted can alter the final concentrations of the active ingredients. The stability of various agents in tinctures can vary based on the concentration, and several extracts of herbs are subject to photodecomposition, suggesting that photoprotective containers may be appropriate for certain TCM preparations [1].

Physicochemical properties, such as those described in the previous paragraph, play a significant role in the interpretation of published data on drug-herb interactions. Fugh-Berman conducted an extensive analysis of studies on herb-drug interactions from 1966 to 1998, and determined that the label on the preparation was the primary source for identification of the herbal component, with correlative analytical information rarely being presented and little information on contaminants or adulterants being provided [34]. Assay interference can also be an issue when analyzing TCM preparations. Zou *et al* identified the presence of significant fluorescence or quenching interference when analyzing various phytochemicals with assays typically used in studies of drug-drug interactions that use complementary DNA-derived cytochrome P450 (CYP) isoforms and fluorogenic substrates [35]. The Herbalome Project in China [36] was created to identify the constituents of approximately 400,000 formulations containing 10,000 herbal and animal tinctures using high-throughput screening, toxicity testing and clinical testing, and this project may contribute to the standardization of assessments of herbal remedies.

Chemical classification and pharmacology of phytochemicals

Interest in determining and understanding the active ingredients in TCM herbal medicines is significant, and this interest has been particularly notable in the past few decades for several reasons, including the determination of pharmacological activity of phytochemicals, the ongoing search for novel sources of synthetic drugs, and documented cases of toxicity and/or interactions with modern therapeutics [37]

Ehrman *et al* classified all phytochemicals in the Chinese herbal constituents database (CHCD) and the bioactive plant compounds database (BPCD) into standard chemical categories, providing justification for the use of herbs in certain indications [38]. For example, alkaloids are representative of compounds that interact with ion channels, GPCRs, and neurotransmitter converters such as AChE and monomine oxidase, indicating possible effects of these compounds in the nervous system. The phenolic or flavonoid content of several herbs has been demonstrated to have beneficial effects in the treatment of cardiovascular

indications, primarily as a result of the antioxidant activity of these compounds [16]. Zhou *et al* studied the popular TCM herb *dan shen* (*Salvia miltiorrhizae*; Radix Salviae Militiorrhizae), which is the dried root of *Salvia miltiorrhiza* and is used extensively in China for the treatment of cardiovascular and cerebrovascular diseases [39]. *Dan shen* provides an instructive example of a single herb that is used in different formulations and is popular worldwide. Formulations of *dan shen* available in China include capsules, tablets, granules, oral liquids, 'dripping pills' or solidified droplets, sprays and parenterals. These formulations are also used for *Fufang Danshen* preparations, which are a combination of *dan shen*, *san qi* (*Panax notoginseng*; Notoginseng Radix) and *zhang nao* (*Cinnamomum camphora*; Camphora). The *Fu Fang Dan Shen* dripping pill has been registered as a drug in several countries, including Vietnam, Korea, Russia, Cuba and Saudi Arabia, and was approved for clinical trials under an IND designation in the US [39]. Approximately 50 compounds have been extracted and identified from *dan shen*, including diterpenes, phenolic acids, baicalin, ursolic acid and daucosterol. The three compounds with the most documented pharmacological activity are danshensu, salvianolic acid B and tanshinone IIA. All three compounds have been demonstrated to be effective in cardiovascular and/or cerebrovascular diseases in animal studies and some human studies [39]. In interaction studies *in vivo*, *dan shen* potentiated the anticoagulant activity of warfarin, and similar results of over-anticoagulation and bleeding were observed in case reports from patients not enrolled in clinical trials [39].

The pharmacological activity of several herbs and herbal formulations used for the treatment of cardiovascular diseases has been associated with the nitrate and nitrite content of the preparations, the ability to reduce nitrite to nitric oxide (NO), and the level of NO deficiency in the disease state [40]. Nitrate and nitrite are known to be physiologically recycled in tissues and the blood to form NO and other biologically active nitrogen oxides. In humans, nitrate is reduced to nitrite by bacteria in the gastrointestinal tract and the skin. Nitrite is relatively stable in the blood and can be further reduced to NO in tissues via hemoglobin, myoglobin, xanthine oxidoreductase, ascorbate, polyphenyls and protons [41]. The generation of NO is enhanced during hypoxia and acidosis, compensating for the compromise of NO synthase-dependent pathways under these conditions. This compensation enhances hypoxic signaling, the modulation of cellular respiratory functioning and vasodilatation – processes that are important in cardiovascular disorders [41].

Databases of herbal and phytochemical compounds

During the past 10 years, several detailed compilations of TCM herbs and phytochemicals have been compiled into searchable databases, such as the CHCD and the BPCD. The CHCD includes 240 Chinese herbs and 8411 compounds, and the BPCD contains 2597 compounds [42]. The Traditional Chinese Medicine Information Database (TCM-ID) from the National University of Singapore contains information on 1588 commonly used prescriptions, 1313 herbs and 5669 herbal ingredients, in addition to the 3D structures of 3725 herbal ingredients [43]. The Comprehensive Herbal Medicine Information System for Cancer (CHMIS-C) from the University of Michigan includes 203 cancer-related molecular targets, 527 anticancer herbal formulations, 937 individual ingredients and 9366 phytochemicals that have been isolated from herbal medicines [44]. These databases represent some of the most comprehensive resources for the constituents of TCM formulations. For example, a search within the TCM-ID for a particular preparation of a herb such as *zhi gan cao* (*Glycyrrhiza uralensis*, *Glycyrrhiza inflata* and *Glycyrrhiza glabra*; Glycyrrhizae Radix praeparata) yields nine phytochemicals identified from *zhi gan cao*, eight of which have associated CAS numbers and 3D structures: glycyrrhetinic acid (CAS number: 471-53-4), rutin (15-18-4), isoquercitrin (21637-25-2), astragalin (480-10-4), ononin (486-62-4), schaftoside (51938-32-0), isoschaftoside (52012-29-0) and narcissin (604-80-8).

CAS numbers, chemical structures and other information obtained from databases can be used with various web-based tools (some requiring registration) to probe the molecular targets, metabolic pathways and potential synergistic and antagonistic effects of constituent phytochemicals. An overlay of phytochemical activities on potential concomitant therapies can alert researchers or practitioners to potential adverse or beneficial interactions with other xenobiotics. Several useful tools are available in this field: the US National Center for Biotechnology Information (NCBI) PubChem [45] and Entrez Gene [46] databases; the Hyleos.net ChemFile Browser [47]; the GeneCards database of human genes [48]; the Universal Protein Knowledge Database [49]; the Kyoto Encyclopedia of Genes & Genomes (KEGG) Pathway Database [50]; the Pharmacogenomics Knowledge Base [51]; Biocarta Pathways [52]; and yEd Graph Editor [53]. Another particularly useful resource is GeneGo Inc's MetaDrug Compound-Based Pathway Analysis web-based software, which is available through a commercial license [54]. This software is a pharmacological systems biology platform that incorporates xenobiotic QSAR (quantitative structure-activity relationship) modeling for CYP, transferase and protein-binding activity, therapeutic activity and toxicity prediction, and includes an extensive manually curated database of the effects and targets of xenobiotics and a meta-search engine.

Examples of the deconvolution of TCM formulations into functional information with the use of online databases are presented in the following section.

Methods for deconvoluting herb-drug interactions

A generalized method for deconvoluting TCM treatment formulations into their constituent phytochemicals, effects on molecular targets, and potential herb-drug

interactions is presented in Figure 1. In the example shown, the database CHMIS-C was used to identify the herbal and chemical constituents of a TCM formulation, and the MetaDrug software was used as a literature meta-search engine and QSAR modeling predictor of the targets and activity of the phytochemicals identified in the TCM formulation. This method can be applied to predict herb-drug interactions, as well as the effects of synergistic or antagonistic activity within a formulation. For example, *dan shen* has been included in an individualized herbal formulation for the treatment of HBV infection that has been molecularly deconvoluted (Tan M: personal communication); the results of this deconvolution are shown in Table 1. In TCM, *dan shen* is believed to eliminate blood stasis and promote blood flow, stimulate menstrual bleeding, relieve pain and inflammation and reduce stress [55]. Studies conducted with extracts of *dan shen* identified the compounds tanshinone I, tanshinone IIA and cryptotanshinone as potent inhibitors of CYP1A2 [56].

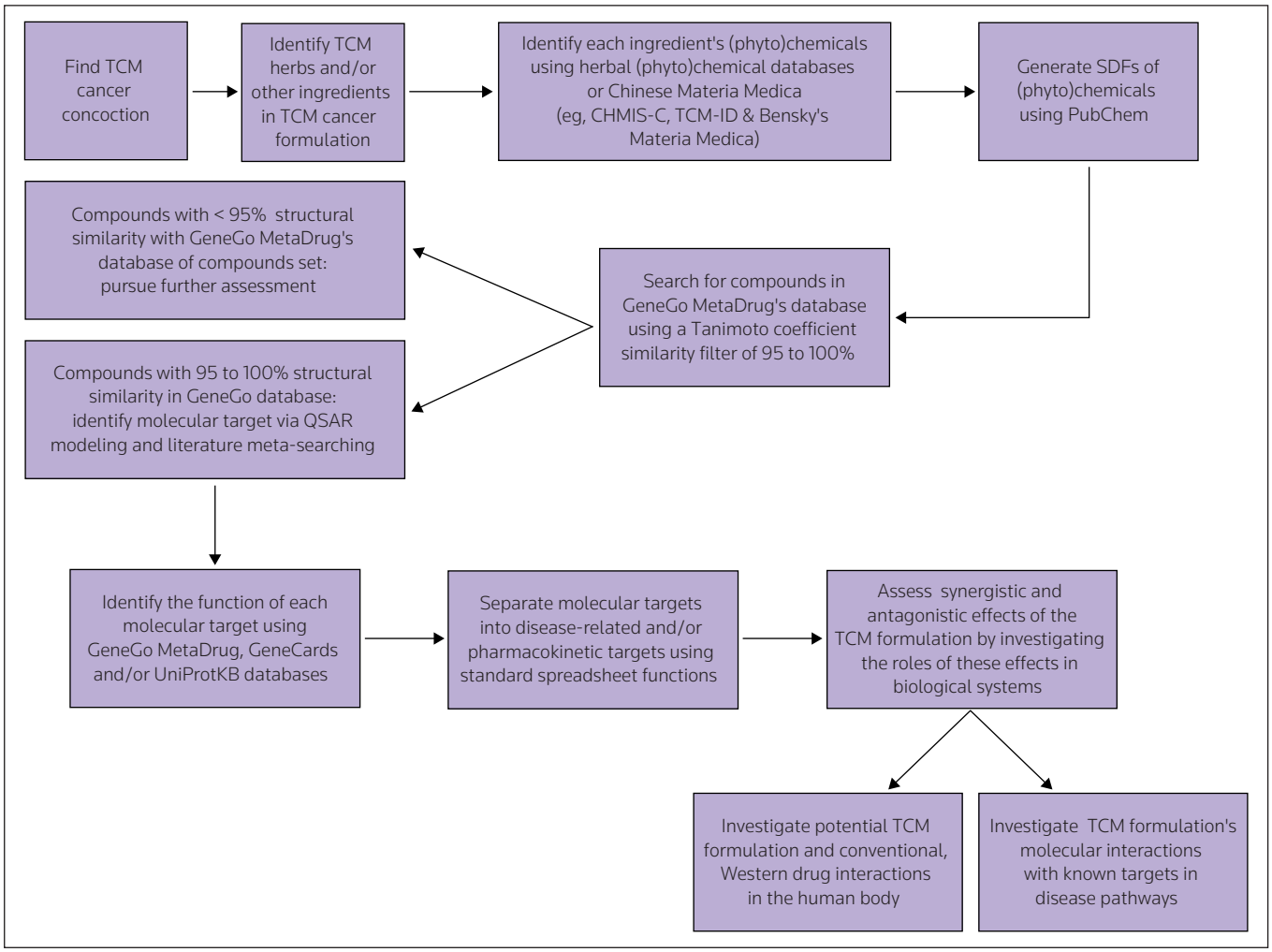
Herbal interactions within traditional Chinese medicine formulations – Synergy and antagonism

Synergism or antagonism between ingredients (ie, herbs and/or phytochemicals) within herbal formulations occurs when two or more ingredients within a concoction mutually enhance or reduce the effect of the formulation in a certain activity or clinical outcome. This effect could result from different actions on the same molecular target (eg, a receptor) or from changes to the bioavailability of active ingredients [19,57].

Examples of synergy between phytochemicals within TCM formulations

Wei Chang An (WCA) is a TCM formulation used for the treatment of gastric cancer. Studies in xenograft animal models demonstrated that WCA induced apoptosis and suppressed cell proliferation in gastric cancer cells by

Figure 1. Deconvoluting TCM formulations into phytochemicals and molecular targets. Scope for predicting TCM formulation-drug interactions.



Bensky's Materia Medica refers to Bensky D (Ed): *Chinese Herbal Medicine: Materia Medica, 3rd edition*. Eastland Press, Seattle, WA, USA (2004).
PubChem refers to the US National Center for Biotechnology Information (NCBI) PubChem (*pubchem.ncbi.nlm.nih.gov*).
CHMIS-C Comprehensive Herbal Medicine Information System for Cancer, **QSAR** quantitative structure-activity relationship, **SDF** structure data file, **TCM** traditional Chinese medicine, **TCM-ID** Traditional Chinese Medicine Information Database

Table 1. Target prediction for *dan shen* based on deconvoluting QSAR methods.

Phytochemical	Molecular target gene	Protein name
Cryptotanshinone	*DGAT1*	Diacylglycerol *O*-acyltransferase 1
Dihydrotanshinone I	*DGAT1*	Diacylglycerol *O*-acyltransferase 1
Hydroxytanshinone IIA	*ACP5*	Tartrate-resistant acid phosphatase type 5
Tanshinone I	*CYP1A2*	CYP1A2
	CYP1A1	CYP1A1
	DGAT1	Diacylglycerol *O*-acyltransferase 1
Tanshinone IIA	*CYP1A2*	CYP1A2
	CYP1A1	CYP1A1
	DGAT1	Diacylglycerol *O*-acyltransferase 1
	ACP5	Tartrate-resistant acid phosphatase type 5
Tanshinone IIB	*ACP5*	Tartrate-resistant acid phosphatase type 5

The compounds listed were all identified in *dan shen* (*Salvia miltiorrhizae*; Radix Salviae Miltiorrhizae; Salvia Root) using the Comprehensive Herbal Medicine Information System for Cancer (CHMIS-C). All of the compounds shown act as inhibitors of the targeted protein. Deconvolution as in Figure 1.
CYP Cytochrome P450, **QSAR** quantitative structure-activity relationship

downregulating the genes *STAT3*, *RUFY3*, *ROD1* and *BCL2* [58]. Tools such as MetaDrug, GeneCards and UniProtKB were used to analyze the molecular targets of WCA, revealing that many WCA phytochemicals promoted apoptosis and the inhibition of cell proliferation via the regulation of cell-cycle control genes and proteins, and also inhibited drug resistance and induced immune and inflammatory responses [48,49,54]. These multiple-endpoint modulations provide evidence for the synergy of phytochemicals within a TCM formulation. Additional examples of synergy between phytochemicals within TCM formulations are listed in Table 2.

Table 2. Examples of synergy between phytochemicals within traditional Chinese medicine formulations.

Function	Herbal ingredient(s) [44]	Target gene name [54]	Target protein name [48,49]
Cell-cycle control	*Scierotium Poriae Cocos*	*CD63*	CD63 molecule
		CDIPT	CDP-diacylglycerol-inositol-3-phosphatidyltransferase
		LTF	Lactotransferrin
		LGALS3	Lectin, galactoside-binding, soluble, 3
		LGALS7	Lectin, galactoside-binding, soluble, 7
		MAPK1 (ERK)	Mitogen-activated protein kinase 1
		MAPK9 (JNK2)	Mitogen-activated protein kinase 9
		MAPK10 (JNK3)	Mitogen-activated protein kinase 10
		MAP2K1 (MEK1)	Mitogen-activated protein kinase kinase 1
		PI4K2A	Phosphatidylinositol 4-kinase type 2 α
		PLCD3	Phospholipase C, δ 3
		PRKCA	PKC, α
		PRKCD	PKC, δ
		PTPRF (LAR)	Protein tyrosine phosphatase, receptor type, F
		RORA	RAR-related orphan receptor A
		SCD	Stearoyl-CoA desaturase (δ-9-desaturase)
		USF2	Upstream transcription factor 2, C-Fos interacting
	Radix Pseudostellariae	*POLB*	Polymerase (DNA directed), β
		POLL	Polymerase (DNA directed), λ
	Spica Prunellae Vulgaris	*PTPN1 (PTP1B)*	Protein tyrosine phosphatase, non-receptor type 1
Drug resistance	*Spica Prunellae Vulgaris*	*ALOX5*	Arachidonate 5-lipoxygenase
	Radix Pseudostellariae, Pericarpium Citri Reticulatae Viride	*ABCB1 (MDR1)*	ATP-binding cassette, sub-family B (MDR/TAP), member 1

Table 2. Examples of synergy between phytochemicals within traditional Chinese medicine formulations. *(Continued)*

Function	Herbal ingredient(s) [44]	Target gene name [54]	Target protein name [48,49]
Drug resistance *(Continued)*	*Radix Pseudostellariae*	*POLB*	Polymerase (DNA directed), β
	Radix Albus Paeoniae Lactiflorae, Scierotium Poriae Cocos, Spica Prunellae Vulgaris, Caulis Sargentodoxae	*TOP2A*	Topoisomerase (DNA) II α 170 kDa
		TOP2B	Topoisomerase (DNA) II β 180 kDa
Immune response	*Scierotium Poriae Cocos*	*CD59*	CD59 molecule, complement regulatory protein
		CD209	CD209 molecule
		CLEC7A	C-type lectin domain family 7, member A
		CTLA4	Cytotoxic T-lymphocyte-associated protein 4
		DEFB1	Defensin, β 1
		CLEC4M	C-type lectin domain family 4, member M
		FN1	Fibronectin 1
		ICOS	Inducible T-cell costimulator
		ICAM1	Intercellular adhesion molecule 1
		LTF	Lactotransferrin
		LCK	Lymphocyte-specific protein tyrosine kinase
		MBL2	Mannose-binding lectin (protein C) 2, soluble (opsonic defect)
		MPO	Myeloperoxidase
		ORM2 (AGP2)	Orosomucoid 2
	Caulis Sargentodoxae	*NOX1*	NADPH oxidase 1
		SELL	Selectin L
	Scierotium Poriae Cocos, Caulis Sargentodoxae	*SELP (CD62)*	Selectin P (granule membrane protein 140 kDa, antigen CD62)
Inflammation	*Spica Prunellae Vulgaris*	*VCAM1*	Vascular cell adhesion molecule 1
		ELANE (ELA2)	Elastase 2, neutrophil
	Radix Albus Paeoniae Lactiflorae	*PRDX5*	Peroxiredoxin 5
	Scierotium Poriae Cocos	*PTGES*	Prostaglandin E synthase
	Spica Prunellae Vulgaris	*PTGS2 (COX2)*	Prostaglandin-endoperoxide synthase 2 (prostaglandin G/H synthase and cyclooxygenase)
Immune response and inflammation	*Caulis Sargentodoxae*	*SELE*	Selectin E
	Scierotium Poriae Cocos	*ORM1*	Orosomucoid 1
	Radix Pseudostellariae, Scierotium Poriae Cocos	*PPARA*	Peroxisome proliferator-activated receptor α

Examples of antagonism between phytochemicals within TCM formulations

Some phytochemicals within WCA inhibit particular molecular targets, while other phytochemicals in WCA activate the same molecular targets. For example, caffeic acid in *xia ku cao* (*Prunellae vulgaris;* Prunellae Spica) inhibits the α-1A-adrenergic receptor, while synephrine in *qing pi* (*Citrus reticulata;* Citri reticulatae viride Pericarpium) activates the same target. Even phytochemicals within the same herbal ingredient have been demonstrated to elicit contrasting effects on a molecular target [44,48,49,54]. For example, two phytochemicals that occur in *fu shen* (*Poria cocos*; Poria), D-glucose and mannose, inhibit and activate MBL2 (mannose-binding lectin [protein C) 2, soluble [opsonic defect]), respectively (data obtained from MetaDrug, GeneCards and UniProtKB). Additional examples of antagonism between phytochemicals within TCM formulations are provided in Table 3.

Table 3. Examples of antagonism between phytochemicals within traditional Chinese medicine formulations.

Target gene [54]	Target name [48,49]	Action [54]	Herbal ingredient [44]	Phytochemical [44]
ADRA1A	α-1A-adrenergic receptor	Inhibition	*Spica Prunellae Vulgaris*	Caffeic acid
		Activation	*Pericarpium Citri Reticulatae Viride*	Synephrine
ABCB1 (MDR1)	ATP-binding cassette, sub-family B (MDR/TAP), member 1	Inhibition	*Radix Pseudostellariae*	Saponin A
		Inhibition	*Pericarpium Citri Reticulatae Viride*	Tangeretin
				5-Demethyl tangeretin
		Activation	*Scierotium Poriae Cocos*	Lecithins
HRH1	Histamine receptor H1	Inhibition	*Scierotium Poriae Cocos*	Histamine
		Activation	*Scierotium Poriae Cocos*	Histidine
MBL2	Mannose-binding lectin (protein C) 2, soluble (opsonic defect)	Inhibition	*Scierotium Poriae Cocos*	D-glucose
		Activation	*Scierotium Poriae Cocos*	Mannose
PYGM	Phosphorylase, glycogen, muscle	Inhibition	*Scierotium Poriae Cocos*	D-glucose
		Activation	*Scierotium Poriae Cocos*	β-D-glucan
PRKCD	PKC, δ	Inhibition	*Scierotium Poriae Cocos*	Lecithins
		Activation	*Scierotium Poriae Cocos*	Histamine

Examples of interactions between TCM and Western drugs

Interactions between phytochemicals/herbal remedies and enzymes that affect drug metabolism and deposition have been described in several studies [1]. The most frequently cited interactions are those involving St John's wort, grapefruit juice and garlic, agents that are used worldwide. Table 4 and Table 5 list various herbs and their actions on specific metabolizing enzymes and/or transporters. Based on the inhibitory or inducing activity of the herbs, the table also includes a list of common drugs that may have herb-drug interaction potential. The examples included in these table are based on well-documented TCM herb interactions with conventional Western drugs.

Table 4. Potential herb-drug interactions with drugs metabolized by CYP1 and CYP2 enzymes.

Protein CYP enzyme	Common drug substrates for CYP enzyme	Interactive effect	Herb-causing effect	Reference
CYP1A2	Clozapine Cyclobenzaprine Imipramine Mexiletine Naproxen Riluzole Tacrine Theophylline	Induction	Green & black/fermented tea (*Camellia sinensis*)	[74,75]
		Inhibition	*Ginkgo biloba*	[65,74,75]
			Scutellaria baicalensis	[54,65,74,75]
			Camomile (*Matricaria recutita*)	[74,75]
			Dandelion (*Taraxacum officinale*)	[74,75]
			Echinacea (*Echinacea purpurea*)	[74,75]
			Frankincense (*Boswellia carterii*)	[65,74,75]
			Grapefruit (*Citrus paradisi*)	[61,74-76]
			Kava (*Piper methysticum*)	[74,75]
			Pepper (*Piper nigrum*)	[61,65,74,75]
			Peppermint (*Mentha piperata*)	[74,75]
			St John's wort (*Hypericum perforatum*)	[61,74-77]
CYP2B6	Bupropion Cyclophosphamide Efavirenz Ifosfamide Methadone	Inhibition	*Scutellaria baicalensis*	[54,65,74,75]
CYP2C8	Amodiaquine Cerivastatin Paclitaxel Repaglinide Torsemide	Inhibition	*Angelica dahurica*	[65,74,75]
			Frankincense (*Boswellia carterii*)	[74,75]
			Grapefruit (*Citrus paradisi*)	[74-76]

Table 4. Potential herb-drug interactions with drugs metabolized by CYP1 and CYP2 enzymes. *(Continued)*

Protein CYP enzyme	Common drug substrates for CYP enzyme	Interactive effect	Herb-causing effect	Reference
CYP2C9	Celecoxib Diclofenac Fluvastatin Glipizide Ibuprofen Irbesartan Losartan Naproxen Phenytoin Piroxicam Rosiglitazone Sulfamethoxazole Tamoxifen Tolbutamide Torsemide Warfarin	Inhibition	*Angelica dahurica*	[65,74,75]
			Ginkgo biloba	[65,74,75]
			Scutellaria baicalensis	[54,65,74,75]
			Camomile (*Matricaria recutita*)	[74,75]
			Frankincense (*Boswellia carterii*)	[65,74,75]
			Goldenseal (*Hydrastis canadensis*)	[74,75]
			Grapefruit (*Citrus paradisi*)	[74-76]
			Green & black/fermented tea (*Camellia sinensis*)	[74,75]
			Kava (*Piper methysticum*)	[74,75]
			Papaya (*Carica papaya*)	[34,74,77]
			Saw-palmetto (*Serenoa repens*)	[74,75]
			Siberian ginseng (*Eleutheroccus senticosus*)	[74,75]
			St John's wort (*Hypericum perforatum*)	[61,74-76]
CYP2C19	Amitriptyline Clomipramine Clopidogrel Cyclophosphamide Diazepam Lansoprazole Omeprazole Pantoprazole Phenobarbitone Phenytoin Progesterone Rabeprazole	Inhibition	*Angelica dahurica*	[65,74,75]
			Ginkgo biloba	[51,65,74,75]
			Scutellaria baicalensis	[54,65,74,75]
			Camomile (*Matricaria recutita*)	[74,75]
			Echinacea (*Echinacea purpurea*)	[74,75]
			Frankincense (*Boswellia carterii*)	[74,75]
			Garlic (*Allium sativum*)	[74,75]
			Goldenseal (*Hydrastis canadensis*)	[74,75]
			Grapefruit (*Citrus paradisi*)	[74-76]
			Green & black/fermented tea (*Camellia sinensis*)	[74,75]
			Kava (*Piper methysticum*)	[74,75]
			Siberian ginseng (*Eleutheroccus senticosus*)	[74,75]
			St John's wort (*Hypericum perforatum*)	[61,74-76]
			Valerian root (*Valeriana officinalis*)	[74,75]
CYP2D6	Amitriptyline Aripiprazole Clomipramine Codeine Desipramine Dextromethorphan Duloxetine Flecainide Haloperidol Imipramine Mexilletine Ondansetron Paroxetine Propafenone Risperidone S-metoprolol Tamoxifen Thioridazine Timolol Tramadol Venlafaxine	Inhibition	*Ginkgo biloba*	[51,65,74,75]
			Scutellaria baicalensis	[54,65,74,75]
			Black cohosh (*Cimicifuga racemosa*)	[65,74,75]
			Echinacea (*Echinacea purpurea*)	[74,75]
			Frankincense (*Boswellia carterii*)	[74,75]
			Goldenseal (*Hydrastis canadensis*)	[74,75]
			Green & black/fermented tea (*Camellia sinensis*)	[74,75]
			Siberian ginseng (*Eleutheroccus senticosus*)	[74,75]
			St John's wort (*Hypericum perforatum*)	[61,74-76]

Table 4. Potential herb-drug interactions with drugs metabolized by CYP1 and CYP2 enzymes. *(Continued)*

Protein CYP enzyme	Common drug substrates for CYP enzyme	Interactive effect	Herb-causing effect	Reference
CYP2E1	Acetaminophen Aniline Benzene Chlorzoxazone Enflurane Ethanol Halothane Isoflurane Methoxyflurane *N,N*-dimethyl-formamide Sevoflurane Theophylline	Inhibition	Garlic (*Allium sativum*)	[74,75]

CYP Cytochrome P450

Table 5. Potential herb-drug interactions with drugs metabolized by CYP3 enzymes and/or transported by MDR1.

Protein CYP enzyme	Common drug substrates for CYP enzyme	Interactive effect	Herb-causing effect	Reference
CYP3A4	Amlodipine Aripiprazole Astemizole Atorvastatin Buspirone Chlorpheniramine Cisapride Diazepam Diltiazem Erythromycin Felodipine Gleevec Haloperidol Indinavir Lovastatin Methadone Midazolam Nifedipine Nisoldipine Nitrendipine Pimozide Quinidine Quinine Ritonavir Saquinavir Sildenafil Simvastatin Tacrolimus Tamoxifen Telithromycin Trazodone Triazolam Verapamil Vincristine	Induction	Guggul (*Commiphora mukul*)	[74,75]
			St John's wort (*Hypericum perforatum*)	[61,74-76]
		Induction (hepatic); inhibition (enteric)	Echinacea (*Echinacea purpurea*)	[74,75]
		Inhibition (enteric)	Bitter orange (*Citrus aurantia*)	[51,65,74,75]
			Grapefruit (*Citrus paradisi*)	[74-76]
		Inhibition	*Angelica dahurica*	[65,74,75]
			Ginkgo biloba	[51,65,74,75]
			Scutellaria baicalensis	[54,65,74,75]
			Asian Ginseng (*Panax ginseng*)	[51,74,75]
			Camomile (*Matricaria recutita*)	[74,75]
			Frankincense (*Boswellia carterii*)	[74,75]
			Goldenseal (*Hydrastis canadensis*)	[74,75]
			Green & black/fermented tea (*Camellia sinensis*)	[74,75]
			Kava (*Piper methysticum*)	[74,75]
			Licorice (*Glycyrrhiza glabra*)	[51,65,74,75]
			Milk thistle (*Sylibum marianum*)	[74,75]
			Pepper (*Piper nigrum*)	[61,65,74,75]
			Pomelo (*Citrus grandis*)	[51,65,74,75]
			Soya Crop	[51,65,75]
CYP3A5	Alprazolam Amlodipine Aripiprazole Astemizole Atorvastatin Buspirone Chlorpheniramine	Induction (hepatic); inhibition (enteric)	Echinacea (*Echinacea purpurea*)	[74,75]
		Inhibition (enteric)	Grapefruit (*Citrus paradisi*)	[74-76]

Table 5. Potential herb-drug interactions with drugs metabolized by CYP3 enzymes and/or transported by MDR1. *(Continued)*

Protein CYP enzyme	Common drug substrates for CYP enzyme	Interactive effect	Herb-causing effect	Reference
CYP3A5 *(Continued)*	Cisapride Clarithromycin Cyclosporine Diazepam Diltiazem Felodipine Gleevec Haloperidol Indinavir Lovastatin Methadone Midazolam Nifedipine Nisoldipine Nitrendipine Pimozide Quinine Ritonavir Saquinavir Sildenafil Simvastatin Tacrolimus Tamoxifen Telithromycin Trazodone Triazolam Verapamil Vincristine	Inhibition	*Angelica dahurica*	[65,74,75]
			Garlic (*Allium sativum*)	[74,75]
CYP3A7	Alprazolam Amlodipine Aripiprazole Astemizole Atorvastatin Buspirone Chlorpheniramine Cisapride Clarithromycin Cyclosporine Diazepam Diltiazem Erythromycin Felodipine Gleevec Haloperidol Indinavir Lovastatin Methadone Midazolam Nifedipine Nisoldipine Nitrendipine Pimozide Quinidine Quinine Ritonavir Saquinavir Sildenafil Simvastatin Tacrolimus Tamoxifen Telithromycin Trazodone Triazolam Verapamil Vincristine	Induction (hepatic); inhibition (enteric)	Echinacea (*Echinacea purpurea*)	[74,75]
		Inhibition	*Angelica dahurica*	[65,74,75]
			Garlic (*Allium sativum*)	[74,75]

Table 5. Potential herb-drug interactions with drugs metabolized by CYP3 enzymes and/or transported by MDR1. *(Continued)*

Protein transporter	Common drug substrates for ABCB1	Interactive effect	Herb-causing effect	Reference
ABCB1 (MDR1, Pgp)	Acetaminophen Cyclosporine Digoxin Efavirenz Erythromycin Fexofenadine Imatinib Indinavir Irinotecan Lansoprazole Midazolam Nevirapine Nifedipine Nitrendipine Omeprazole Ondansetron Paclitaxel Pantoprazole Phenytoin Risperidone Ritonavir Saquinavir Sertraline Simvastatin Tacrolimus Tamoxifen Verapamil Vincristine Warfarin	Induction	Garlic (*Allium sativum*)	[51,74,75]
			Guggul (*Commiphora mukul*)	[51,74,75]
		Induction (enteric)	St John's wort (*Hypericum perforatum*)	[51,61,74,75]
		Inhibition	Asian Ginseng (*Panax ginseng*)	[51,65,74,75]
			Milk thistle (*Sylibum marianum*)	[51,74,75]
			Pepper (*Piper nigrum*)	[51,61,65,74,75]
			Valerian root (*Valeriana officinalis*)	[51,74,75]
		Modulation	*Ginkgo biloba*	[65,74,75]

CYP Cytochrome P450

The herb *dang gui* (*Angelica sinensis*; Angelicae sinensis Radix), which is also known as *dong quai*, *tangkuei* and female ginseng, is used in many premenstrual, menopausal and other gynecological TCM treatments; the root of this herb has also been used to treat fatigue, anemia and high blood pressure. Pharmacological properties of this herb have been attributed to constituent coumarins, polysaccharides, ferulate and/or flavonoids, with some of these constituent components demonstrating antithrombotic and antiarrhythmic activities [59,60]. In a clinical setting, the concurrent use of *dang gui* and warfarin has been reported to potentiate the anticoagulant effects of warfarin, to increase the international normalized ratio (INR) and to promote widespread bruising [34,60-62]. Considering these factors, the use of *dang gui* with other blood-thinning agents (anticoagulants, platelet inhibitors and thrombolytic agents), aspirin or other NSAIDs is contraindicated [63,64].

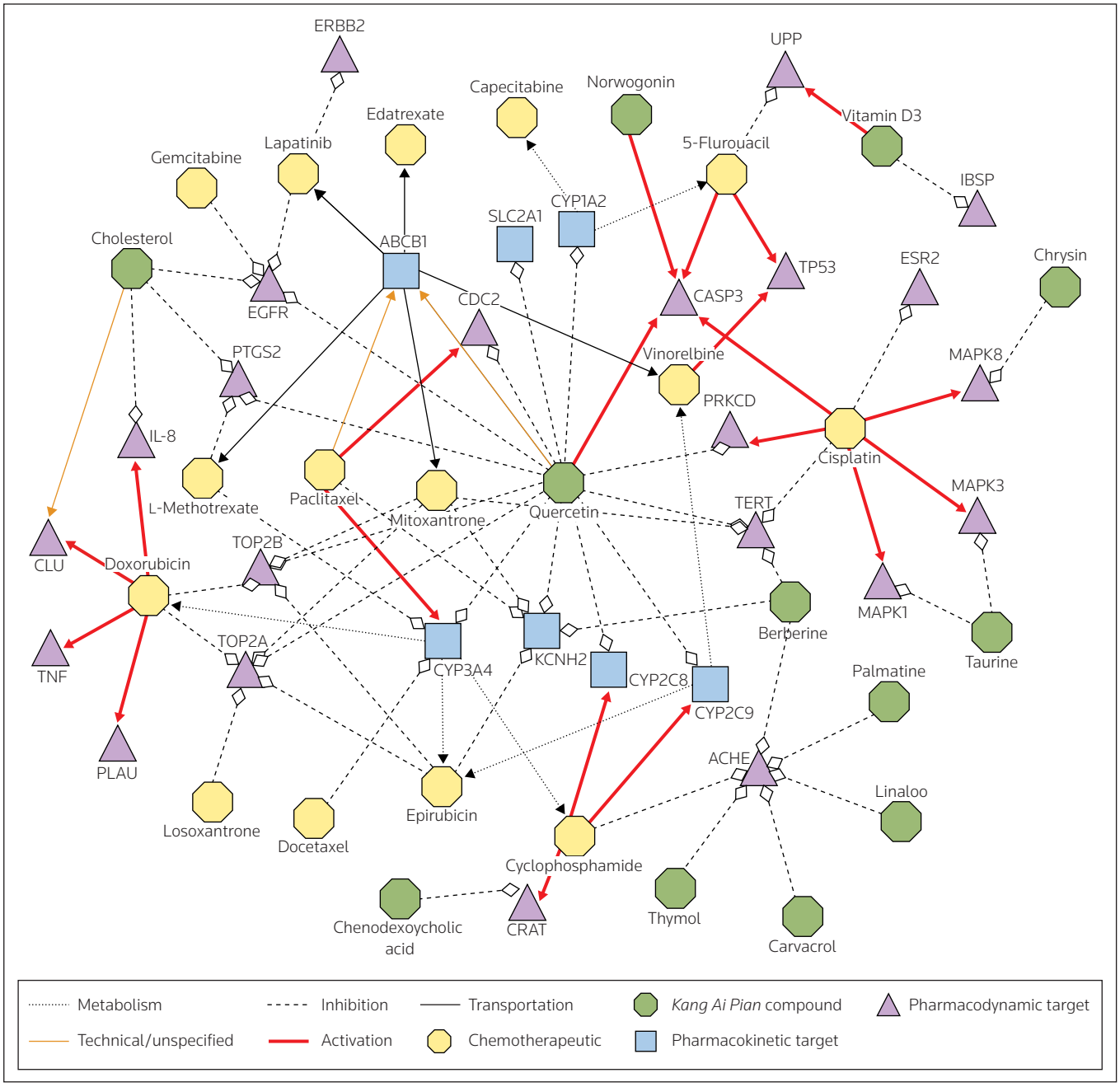
Licorice root, known as *gan cao* in Chinese, is the most commonly used compound in TCM formulations [65]. TCM often uses three different species of licorice interchangeably: Chinese licorice or *Glycyrrhiza uralensis* (*gan cao*; the most commonly used), *Glycyrrhiza inflata* (*zhang guo gan cao*; the second most commonly used) and *Glycyrrhiza glabra* (*guang guo gan cao*; the third most commonly used, and the species used in Western candy production and the Western health market). TCM also uses the species *Glycyrrhiza eurcarpa* (*huang gan ca*) and *Glycyrrhiza aspera* (*cu mao gan cao*) as alternatives [15,66].

Licorice contains triterpenes, such as glycyrrhizic acid, flavonoids, alkaloids, coumarin derivatives, isoflavonoids and chalcones [65,67]. Glycyrrhizic acid or glycyrrhizin, which is the main constituent of licorice responsible for sweetness, has been reported to have antiviral activity against several unrelated DNA and RNA viruses, including HBV and respiratory viruses [68,69]. In addition, glycyrrhizic acid has been demonstrated to exert hepatoprotective properties against xenobiotic-induced toxicity and hepatocellular damage in chronic hepatitis B conditions [68,70,71]. The use of licorice as a messenger drug to improve systemic drug delivery may be the result of the inhibitory effects of this herb on intestinal P-glycoprotein or on the multidrug resistance transporter protein ABCB1, effects that could promote increased bioavailability of other phytochemicals [72]. Licorice has been demonstrated to decrease the clearance of prednisolone and to increase prednisolone bioavailability when taken in combination with this drug [34,73]. Licorice has also been reported to potentiate the cutaneous vasoconstrictor response of hydrocortisone. In total,

more than 100 drugs are known to interact with licorice, including corticosteroids, antihypertensives, diuretics, laxatives and other potassium-depleting drugs [73]. However, most of these interactions are modest in severity.

Kang Ai Pian is a TCM formulation used to treat cervical, ovarian, breast, nasopharyngeal, lung, liver and gastrointestinal cancer. *Kang Ai Pian* is comprised primarily of *chen pi* (*Citrus reticulata*; Citri reticulatae Pericarpium), *huang bo* (*Phellodendron amurense*; Phellodendri Cortex), *huang lian* (*Coptis chinensis*, *Coptis deltoidea* and *Coptis teeta;* Coptidis Rhizoma), *huang qin* (*Scutellaria baicalensis*; Scutellariae Radix), *hu po* (*amber*; Succinum), *niu huang* (*Bos taurus domesticus*; Bovis Calculus) and *san qi* (*Panax notoginseng*; Notoginseng Radix) [44]. The network scheme depicted in Figure 2 was generated

Figure 2. Potential drug-herb interactions between *Kang Ai Pian* and chemotherapeutic agents.



Kang Ai Pian is a traditional Chinese medicine formulation that is used in the treatment of several forms of cancer, and consists primarily of *chen pi* (*Citrus reticulata*; Citri reticulatae Pericarpium), *huang bo* (*Phellodendron amurense*; Phellodendri Cortex), *huang lian* (*Coptis chinensis*, *Coptis deltoidea* and *Coptis teeta*; Coptidis Rhizoma), *huang qin* (*Scutellaria baicalensis*; Scutellariae Radix), *hu po* (*amber*; Succinum), *niu huang* (*Bos taurus domesticus*; Bovis Calculus) and *san qi* (*Panax notoginseng*; Notoginseng Radix) [44].
ACHE Acetylcholinesterase, **CASP3** caspase 3, **CLU** clusterin**, CRAT** carnitine *O*-acetyltransferase, **CYP** cytochrome P450, **ESR2** estrogen receptor 2 (also known as ERβ), **IBSP** integrin-binding sialoprotein, **KCNH2** potassium voltage-gated channel, subfamily H (EAG-related), member 2 (also known as hERG ion channel), **PLAU** plasminogen activator, urokinase, **PRKCD** PKC δ, **PTGS2** prostaglandin G/H synthase 2, **TOP2A** DNA topoisomerase 2α.

using the deconvoluting method, as presented in Figure 1, and illustrates the potential herb-drug interactions of *Kang Ai Pian* when used concomitantly with 15 different Western chemotherapy treatments. As with many TCM preparations or complementary/alternative treatments, medical practitioners may not have been informed that such combinations are being used. Thus, full disclosure of all medications by the patient is highly desirable.

Conclusion

The use of herbal preparations either as dietary supplements or as part of a traditional medicine approach is increasing worldwide. The increased controls on the ingredients and the labeling used in such preparations, as observed in certain regions such as Japan, will enable a more rational use of these products and improve the understanding among both medical practitioners and patients. In the US, where these products are considered to be dietary supplements and where there are no established methods of labeling or quality control, the issue of potential herb-drug interactions remains a concern. Currently, a consumer in the US may buy several of the herbal preparations listed in this review, and might view promotional disease-related labeling that includes caveats such as 'this label has not been approved by the FDA' and 'this product is not to be used to treat or diagnose a disease'. Several of these preparations have been demonstrated to interact with important molecular targets, and therefore this relatively unknown and mostly unreported form of polypharmacy (eg, when the use of these products is combined with Western drugs) exists in the majority of healthcare systems in developed countries. The emergence of an integrated medicine approach in healthcare centers, where TCM and Western treatment modalities are being used in combination, as well as the growing abundance of searchable databases and informatics research tools, will continue to emphasize the importance of evidence-based research and the availability of information on the potential efficacy and safety of phytochemical constituents in herbs and TCM formulations. Combination therapies being assessed in clinical trials include those for various allergies, hepatitis, diabetes and cancer, for which the main focus is on balancing the immune system with phytochemicals to increase tolerance to chemotherapy.

This review discusses a method to deconvolute TCM formulations into constituent phytochemicals, thus identifying potential molecular targets with proposed biologically relevant activity. This approach could form the basis for rational hypotheses and assist in determining priorities for research on herb-drug interactions.

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