The Role of Traditional Chinese Herbal Medicines in Cancer Therapy – from TCM Theory to Mechanistic Insights

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Abstract

Traditional Chinese medicine-based herbal medicines have gained increasing acceptance worldwide in recent years and are being pursued by pharmaceutical companies as rich resources for drug discovery. For many years, traditional Chinese medicines (TCM) have been applied for the treatment of cancers in China and beyond. Herbal medicines are generally low in cost, plentiful, and show very little toxicity or side effects in clinical practice. However, despite the vast interest and ever-increasing demand, the absence of strong evidence-based research and the lack of standardization of the herbal products are the main obstacles toward the globalization of TCM. In recent years, TCM research has greatly accelerated with the advancement of analytical technologies and methodologies. This review of TCM specifically used in the treatment of cancer is divided into two parts. Part one provides an overview of the philosophy, approaches and progress in TCM-based cancer therapy. Part two summarizes the current understanding of how TCM-derived compounds function as anticancer drugs.

Abbreviations

AFAP-1:	actin filament-associated protein 1
AIF:	apoptosis-inducing factor
BAD:	Bcl-2-associated death promoter
BAK:	BCL2-antagonist/killer
BAX:	BCL2-associated X protein
BCL2:	B cell leukemia/lymphoma 2
BCL-XL:	B cell leukemia/lymphoma xL
BID:	BH3 interacting domain protein
BIM:	Bcl-2 interacting mediator
Casp3:	caspase 3
Casp6:	caspase 6
Casp7:	caspase 7
Casp8:	caspase 8
Casp10:	caspase 10
cytoC:	cytochrome C
ERK1/2:	extracellular signal-regulated kinase 1/2
FADD:	FAS-associated death domain
FASL:	FAS ligand
FOXO1:	forkhead box 1
Gp130:	glycoprotein 130
GRB2:	growth factor receptor-bound protein 2
HER2:	human epidermal growth factor receptor 2
IκB:	IkappaB
IKK:	IkappaB kinase
IL-6:	interleukin-6
IL-6R:	interleukin-6 receptor
JAK:	Janus kinase
MCL-1:	myeloid cell leukemia sequence 1
MDM2:	murine double minute 2
MEK1/2:	MAP kinase kinase 1/2
MMP:	matrix metalloproteinase
Mule:	Mcl-1 ubiquitin ligase E3
NF-kB:	nuclear factor-kappaB
NIK:	MEK kinase 14
p90RSK:	p90 ribosomal S6 kinase
PARP:	poly (ADP-ribose) polymerase
PI3K:	phosphoinositide 3-kinase
PIP3:	phosphatidylinositol 3,4,5-trisphosphate
PUMA:	p53 upregulated modulator of apoptosis
SH2:	Src-homology 2
SOS:	son of sevenless
STAT3:	signal transducer and activator of transcription 3
t-BID:	truncated BH3 interacting domain protein
TIMP:	tissue inhibitor of matrix metalloproteinase
TNFαR1:	TNF-alpha R1
TNFαR2:	TNF-alpha R2
Topo I:	topoisomerase I

Topo II: topoisomerase II
TRADD: TNFRSF1A-associated death domain
TRAF2: TNF receptor-associated factor 2
TRAIL: TNF-related apoptosis-inducing ligand
TRAILR: TRAIL receptor
VEGF: vascular endothelial growth factor
VEGFR: vascular endothelial growth factor receptor
XIAP: X-linked inhibitor of apoptosis protein

Introduction

TCM views of cancer and the approach toward cancer treatment

Cancer is one of the major causes of mortality in humans throughout the world. According to a report dealing with the incidence and mortality of cancers in the USA, a total of 1 479 350 new cancer cases and 562 340 deaths from cancer were projected to occur in 2009 [1]. For cancer treatment by conventional medicine, surgery, chemotherapy and radiotherapy have been the primary approaches, but they are not always effective. As of today, cancer is still the most threatening and difficult to treat disease.

Cancerous conditions are well-known in the traditional Chinese medical system. In the classics of TCM, "Huang Di Nei Jing Di" (黃帝內經) published more than 2000 years ago, there are descriptions of the pathogenesis, appearances and treatment principles of tumors (瘤), such as muscle, tendon and bone carcinomas; however, this term does not differentiate between malignant and nonmalignant tumors. It was not until the Sung Dynasty (ca. 1300 AD) that the first reference to cancer – the Chinese word Ai (癌) meaning malignant carcinoma – first appeared in the ancient medical book "Wei Ji Bao Shu" (衛濟寶書). According to the theories of TCM, cancer is caused by imbalances between endogenous physical conditions of the body and exogenous pathogenic factors. The internal condition of the body plays a dominant role in the onset of cancer. In other words, factors can induce cancer only when the body's own defense system fails. Those pathogenic factors, in Chinese medicine terms, include accumulated toxins, heat and blood stasis, and they attack when a person is in a weak physical condition, without the strength to resist. Furthermore, malfunction of the body-mind communication network may also trigger the development of cancer [2]. So, TCM doctors view cancer as a systemic disease associated with the state of the whole body (or disturbance of the signaling network, to use a modern term). "Systemic" in the TCM doctors' views, means "state of the whole body". "Cancer is the manifestation of a breakdown in the body's ability to handle pathogenic factors, not a local disease of cells or organs." Accordingly, the treatment philosophy and strategy of TCM emphasizes holistic modulation and improvement of the whole body rather than removing the tumor mass or killing the cancerous cells. This treatment strategy is particularly enforced for cancer patients at the late stages. In these stages, the focus of treatment is extending the life expectancy and improving the quality of life of the patient; in other words, the focus is on the patient not the tumor mass (帶瘤生存).

The other major principle of TCM is the emphasis on an individual therapy. For the same type of cancer in different persons, the diagnosis and treatment schemes could be very different. This is called the principle of "treatment based on symptom pattern differentiation (辨證論治)". In other words, TCM doctors make the diagnosis and prepare a treatment scheme based on the assessment of the pattern of symptoms manifest in each individual. When herbs are called for, most commonly, several are used together, and the whole herbs are used, not purified compounds. Thus, in the prescription, there will be multiple effective components delivering a comprehensive, integrated treatment of cancer through multiple targets and their associated pathways. This approach is in line with the view of TCM that cancer is a systemic disease that requires a holistic approach and medicines that can produce therapeutic actions through multiple targets. While this approach differs from that of conventional medicine, the effects of treatment still come down to biochemistry. If treatments are effective, then there must be underlying mechanisms that can be investigated and verified scientifically. Understanding these mechanisms can help us expand the efficacy of both Western and Chinese medicines in a logical, rational way.

Evaluation of the Therapeutic Effects of TCM Herbal Medicines in Cancer Treatment – The Benefits and the Obstacles

To provide the scientific basis for the effectiveness of TCM against cancer, a number of clinical and laboratory studies have been done in the past decades. However, due to various factors – including inconsistency in treatment schemes, the limited sampling sizes, and lack of quality assurance of the herbal products – well-designed randomized controlled trials (RCT) to prove the effectiveness of TCM as adjuvant therapy for cancer are scarce. In general, most of the published clinical studies are at evidence level III; in other words, they were trials without rigorous randomization or they involved single group pre-post, cohort, time series, or matched case-control studies [3]. As a result, there are a number of contradictory reports regarding the therapeutic effectiveness of TCM on the treatment of cancer.

In TCM prescriptions, herbs are generally used in combination as 'formulas', in the belief that the combinations enhance their benefits and simultaneously reduce side effects. With proper diagnosis and understanding of the component herbs, practitioners can adjust or customize the formulas to suit individual cancer patients. Through synergistic interactions between different effective ingredients, the herbal preparation, according to the clinical experiences, can exert its effects in several ways: (i) they can protect the noncancerous cells and tissues in the body from the possible damage caused by chemo/radiotherapy; (ii) they can enhance the potency of chemo/radiotherapy; (iii) they can reduce inflammatory and infectious complications in the tissues surrounding the carcinoma; (iv) they can enhance immunity and body resistance; (v) they can improve general condition and quality of life; and (vi) they can prolong the life span of the patients in the late stages of cancer (**Fig. 1**). So, for an evaluation of the effect and benefit of TCM therapy for cancer patients, all of these above-mentioned aspects need to be considered. A typical example of the synergistic, complex function of the herbs has been given in the study of PHY906, a Chinese herbal preparation made from the herbs of *Scutellaria baicalensis, Paeonia lactiflora, Ziziphus jujuba* and *Glycyrrhiza glabra*. PHY906 is derived from a classic herbal formula used for treatment of diarrhea and inflammatory conditions. Based on the properties and functions of Chinese medicinal herbs, each formula has a principle herb and adjuvant herbs. Here, the *S. baicalensis* acts as a principle herb,

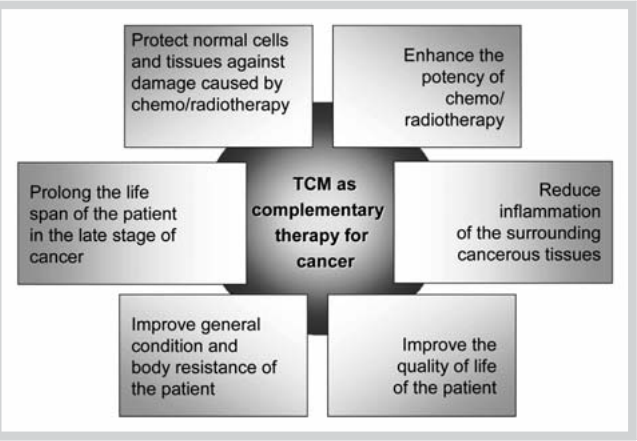

Fig. 1 Schematic presentation of the actions of TCM as adjuvant cancer therapy based on the theory and clinical practice of TCM.

while the rest of the herbs in the formula are assistant herbs. The phase I/IIA randomized clinical study of PHY906 demonstrated a reduction of gastrointestinal toxicity and enhancement of the tumoricidal effect of the chemotherapy in patients with advanced colorectal cancer [4]. Recently, it has been also found effective in increasing the therapeutic efficacy and reducing adverse effects of the cytotoxic drug capecitabine in patients with advanced hepatocellular carcinoma in a phase I/II clinical study [5]. Further animal study demonstrates that removing one or three herbs from the PHY906 formulation would dampen the effect of PHY906 in antitumor activity, reduces toxicity, and reduces the bioavailability of the principle herb (personal communication from Y.C. Cheng). Other than this, many studies have demonstrated that specific combinations of medicinal herbs can be synergistic with cytotoxic chemotherapy through both pharmacodynamic and pharmacokinetic interactions. In a cohort study, a combined treatment of traditional Chinese medicine and Western medicine (WM) or treatment with WM alone was conducted on 222 patients with stage II and III colorectal cancer after radical operation. The survival of WM alone and the WM and TCM combined treatment is 16 months and 26.5 months, respectively, in which WM was administrated as the routine protocol while a TCM formula was given according to the treatment principle of differentiation for symptom patterns [6].

In the past decade, there have been a few systematic reviews regarding the clinical trials against various cancers treated with a TCM formula. One systematic review on colorectal cancer showed that TCM therapy alone or in combination with chemotherapy is useful during the postoperation period in relieving intestinal obstruction, reducing postoperative ileus symptoms and urinary retention [7]. Another systematic review evaluating randomized clinical trails (RCT) of TCM oral therapy for hepatocellular cancers found that many RCTs, although the herbs they studied were effective, were not randomized [8]. With respect to non-small cell lung cancer (NSCLC), although it is one of the common cancers with the highest death rate, there are few reliable reports assessing TCM therapy. One RCT study done in China analyzing the survival time, Karnofsky score, clinical symptoms and adverse reactions shows that chemotherapy plus Kangliu Zengxiao Decoction (KLZXD) is able to prolong the survival time of patients up to 15.57 months versus 11.17 months in the patients treated with chemotherapy alone. The symptoms of fatigue and dyspnea and the adverse effects of leukopenia and dyspepsia caused by chemotherapy were reduced by treatment with KLZXD [9]. However, another study comparing the efficacy of TCM and chemotherapy against NSCLC found uncertain results. Nevertheless, TCM treatment seems to stabilize the tumor mass, relieve clinical symptoms, and elevate quality of life. It is also inexpensive and more convenient compared with the conventional chemotherapy [10]. With regard to advanced breast cancer, the herbal preparation Shenqi Fuzheng Injection (SFI), was demonstrated to alleviate bone marrow inhibition and cellular immunity suppression caused by chemotherapy, and to relieve clinical symptoms, raise the quality of life and prolong survival time compared to patients receiving only chemotherapy [11]. Similarly, a systematic review on nasopharyngeal carcinoma (NPC) suggests that TCM therapy is efficacious as a concomitant therapy for NPC patients, but rigorous controlled clinical trials are still required to confirm these results [12]. A report on TCM therapy for progressive gastric cancer shows some benefits to the patient but the study was not well designed, hence its conclusions are suspect [13]. Unfortunately, a systematic review on esophageal cancer shows no evidence to support the effectiveness of TCM therapy [14]. Based on the above reports, the efficacy of TCM therapy in cancers is still unproven by the current RCT standards.

Aside from the therapeutic effect of TCM therapy on suppressing cancer growth, other potential benefits to patients, such as enhancement of organ functions, improvement of quality of life, reduction of clinical symptoms including pain, and reduction of adverse effects of chemo-/radiotherapy are the indexes closely associated with the characteristics and advantages of TCM treatment as a supplementary remedy to the conventional chemo-/radiotherapy and those indexes have not always been taken into consideration in assessing the therapeutic outcome of TCM in RCT evaluations. For instance, a review analyzing the effectiveness of TCM for liver protection and chemotherapy completion among cancer patients shows that although there is no significant difference in outcome between the TCM-treated and the control groups, TCM therapy alongside the standard chemotherapy resulted in protection of liver function during the course of chemotherapy, as manifested by lower serum AST and ALT levels [15]. As we know, normal liver function is critical for successful completion of a standard course of chemotherapy. Thus, protection of liver function will not only protect the liver organ itself but will also enhance the cytotoxic potency of chemotherapeutic drugs. A systematic review on huangqi decoction in alleviation of chemotherapy side effects in colorectal cancer patients was recently reported [16]. Despite the low quality of the clinical studies, the results suggest that huangqi decoction may stimulate immunocompetent cells and decrease side effects in patients treated with chemotherapy. In addition to the alleviation of chemotherapy side effects, a reduction in cancer pain may also be a beneficial result from TCM treatment according to a recent systematic reviews of 115 articles on clinical research in TCM treatment for cancer pain management [17].

In recent years, improvement of quality of life and prolongation of survival time of cancer patients, whether the cancerous carcinoma disappears or not in the body, have become important factors for evaluating the benefits of any intervention for cancer patients. Another recent study evaluated the effect of the combined Ganji Recipe therapy with the Fructus Bruceae oil emulsion (FBE) intervention or the transhepatic arterial chemical embolization (TACE) on the quality of life and survival time of patients with advanced primary hepatic cancer. The results showed significant

improvements in the quality of life and the life expectancy of the patients receiving Ganji and FBE treatment compared to patients treated with TACE or the Fructus Bruceae oil emulsion intervention alone [18]. Studies on non-small cell lung cancer indicate that TCM therapy is able to markedly reduce the adverse postradiation reactions and improve the quality of life of patients through intensive analysis using QLQ-C30, LC13, QLQ-C30 and LC30 questionnaires [19]. In another cohort study, the herbal preparation of Quxie Capsule was demonstrated to be effective in improving significantly the quality of life and in prolonging the survival of advanced colorectal cancer patients in an RCT study [1].

Molecular Mechanisms of TCM-Based Herbal Medicines as Anticancer Drugs

Proponents of Chinese traditional medicines point out that these medicines, unlike Western drugs in which the therapeutic effects are derived from a single compound with a well-defined target, have synergistic pharmacological effects because each herbal formula consists of several herbs, each with specific therapeutic activities toward the disease or symptoms. Nonetheless, the majority of reports in the literature have taken a reductionist approach, namely working on mostly the TCM-derived pure compounds; few have studied extracts derived from a single herb, and very few have studied TCM formulations which are the form that have historically given the most benefit. At the time of this review, there were two comprehensive reviews published in 2003 on antitumor agents from TCM, focusing on both the chemical properties and the mechanisms of action of those compounds [20,21]. Therefore, this second part of the review will only touch upon a few studies in or before 2003, and will mainly cover reports after 2003 that appeared in the databases, including Ovid MEDLINE®, AMED, CDSR, ACP Journal Club, DARE, CCTR, CLCMR, CLHTA, CLEED, EMBASE-DP, Global Health, restricted to TCM-based herbal medicines. **Table 1** summarizes the articles selected out of ~500 original works on anticancer herbal medicines that meet the criteria mentioned above, i.e., (i) the article describes work on TCM-derived herbal medicine(s), and (ii) it is a mechanistic study at the molecular level. Due to the enormous volume of reports on apoptosis, this review in this area of study will mainly cover reports since 2006. In the review, we will also try to link the current understanding of anticancer TCM herbs based on the experimental and clinical studies with the understanding of the functions of the herbs based on TCM theory and concepts as developed during more than a thousand years of clinical experiences.

Anticancer Effects and Underlying Mechanisms of TCM-Derived Compounds or Herbal Extracts

The anticancer herbal drugs can be divided into three categories based on their target: (i) drugs that uniquely target topoisomerases (Topos) and perturb DNA replication; (ii) drugs that kill tumor cells through apoptotic pathways; and (iii) drugs that alter signaling pathway(s) required for the maintenance of transforming phenotypes of the tumor cells. It is known that many natural products extracted from medicinal herbs show a direct killing effect on tumor cells. There is no exception for the compounds isolated from various traditional Chinese medicines claimed to have anticancer effects. Drugs targeting topoisomerase I & II (Topo I & II) as well as on pro-apoptotic pathways are known to induce cell death. *Camptotheca acuminata* (Xi Shu) is a TCM herb commonly used for cancer treatment in China. The compound camptothecin (CPT) isolated from the plant has been found to uniquely target Topo I, an enzyme which produces a DNA single-strand break in DNA replication. Interference of Topo I induces apoptosis and cell cycle perturbations [22–25]. This finding along with the discovery of natural product-derived taxol have been considered as historic achievements in natural products and have subsequently led to the identification of a series of TCM-derived compounds targeting Topo I & II (**Table 1**).

Apoptosis is a common mode of action of chemotherapeutic agents, including the natural product-derived drugs [26,27]. It appears that this is true for TCM-derived compounds and their extracts. As shown in **Table 1**, 85 out of 104 independent studies of herbal medicines derived from 62 different TCM-based herbal plants revealed that apoptosis is the key mode for cell killing in a wide variety of cancer cells upon the treatment with various tested herbal medicines. For example, solanine, a steroid alkaloid isolated from *Solanum nigrum* Linn. that is a TCM commonly used in treating digestive system cancer, was found to possess anticancer effects and induce apoptosis mediated by the inhibition of the expression of Bcl-2 pro-apoptotic protein [28]. The *Antrodia camphorata* crude extract (ACCE), an extract obtained from a rare traditional Chinese herbal medicine Zhan-Ku (a camphor tree mushroom), has shown rather significant inhibitory effects on the growth of various transitional cell carcinomas (TCC) including RT4, TSGH-8301, and T24 cell lines. Interestingly, at high concentrations, ACCE causes p53-independent overexpression of p21 with simultaneous down-alteration of pRb and senescence in RT4 cells. On the other hand, ACCE at a low concentration simultaneously downregulated Cdc2 and Cyclin B1 with suppression of the absolute migrating capability of the two cell lines TSGH-8301 and T24, and eventually caused cell death [29]. The concentration-dependent cellular responses seem to provide a new avenue to explore the anticancer effects of TCM, especially at nontoxic dosages. The dried root of *Astragalus membranaceus* (Huangqi) has a long history of medicinal use for immunodeficiency diseases and a relatively short history of equal effectivity for alleviating the adverse effects of chemotherapeutic drugs. Total *Astragalus* saponins induce growth inhibition and apoptosis in colon cancer cell line HT-29 and the xenograft [30]. Artemisinin is the active principle isolated from a well-known TCM herb, *Artimisia annua* L. an effective antimalaria drug. Later, studies showed that artemisinin and its derivatives have profound anticancer effects as assessed both in *in vitro* and *in vivo* models [31]. Artesunate, a derivative of artemisinin was found to inhibit angiogenesis and induce apoptosis through p53-dependent and independent pathways. The drug also inhibits NF-kappaB and downregulates the anti-apoptotic Bcl-2 while it activates the pro-apoptotic Bax. *Coptidis rhizoma* (huanglian) and its major active component, berberine, were the most extensively studied herb of the last decade. Berberine as well as Huanglian show diverse biological activities, including antibacterial, anti-inflammatory, antiangiogenesis and pro-apoptotic activities [32]. A recent study elegantly demonstrated that berberine directly targets and modifies cysteine 179 of IkappaB kinase (IKK), leading to the downregulation of NFkappaB and its series of target genes in anti-apoptosis, cell proliferation, inflammation and invasion [33]. There are two major pathways by which chemotherapeutic agents can induce apoptosis of the treated cells. One is known as the mitochondria-mediated pathway, which is activated by cyto-

Table 1 Examples of anticancer compounds or extracts derived from traditional Chinese herbal medicines with known molecular mechanism of action.

Affected molecules and pathways	*In vitro* and/or *in vivo* system	Main TCM herbs	Active component*	Type of compound	Ref.
Topoisomerase I & II inhibitors					
► ↓ Topo I	cancer cells	*Camptotheca acuminata*[5]	camptothecins	alkoloid	[22, 52]
► ↓ Topo II	CHO cells	Chan'su[5]	bufalin	cardiac steroid	[53]
► ↓ Topo I & II & other targets				low molecular weight	[20]
► ↓ Topo II		*Poria cocos*[3]	dehydroebriconic acid	triterpenoid	[54]
► ↓ Topo I & II; ↑ ERK, JNK; → apoptosis	hepatoma cells	*Ganoderma*[3]	genodermic acid	triterpenoid	[55]
► ↓ Topo I	*in vitro* assays	*Daphne genkwa*[5]	yuanhuacines	diterpenoid	[56]
► ↓ Topo II, ROS	cells, & xenografts		salvicine	diterpenoid	[57]
► HER2, TNFR, Fas; ↓ DNA synthesis; → apoptosis	lung cancer cell lines	*Solanum*[1]		alkaloid	[58]
► Antioxidant; ↓ NF-kappaB, Cox-2, PLase C & Ca^{++} signaling	various cancer cell lines	*Scutellaria*[1]	wogonin, baicalein, baicalin	flavones	[59]
► ↓ Topo I & II, NF-kappaB, AP-1; ↑ p53; ↓ STAT3, IGF1R, HER2		Many	luteolin	flavonoids	[60]
Apoptosis					
► ↑ p21 & ↓ cyclin D1	breast cancer cells MDA-MB-231	*Coriolus versicolor*[3]	polysaccharides peptide	polysaccharides	[61]
► Microarrays-detected genes	H lung cancer A549 cells	*Scutellaria barbata*[1]	crude extract	naphthoquinone	[62]
► ↓ Telomerase & Bcl-2, ↑ Bax	leukemia K562	*Rabdosia rebescens*[1]	oridonin	diterpene	[63]
► ↓ Bcl-2	Hep3B	*Scutellaria barbata*[1]	pheophrbide		[64]
► ↓ Bcl-2, ↑ p53 & PARP-1	MCF-7	*Curcuma xanthorrhiza*[2]	xanthorrhizol	sesquiterpenoid	[65]
► ↓ Bcl-2/Bcl-XL	MCF-7	*Patrinia scabiosaefolia*[1]	not known	crude extract	[66]
► ↑ Caspases & Bax	prostate PC-3	*Alismatis rhizoma*[4]	alisol B acetate	triterpene	[67]
► ↓ Bcl-2, ↑ Caspases & Bax	lung cancer cells	*Rabdosia rebescens*[1]	ponicidin	diterpenoid	[68]
► ↑ PARP, caspase-3	leukemia K562	*Sophora flarescens* Ait.[1]	matrine	alkaloid	[69]
► ↑ Caspase-8, with trail	cholangiocarcinoma TRAIL-resistant cells	*Tripterygium wilfordii*[5]	triepolide	diterpene	[70]
► Cdk inhibitor	chronic myelocytic leukemia	*Danggui longhui* Wan#	indirubin	alkaloid	[71]
► ↓ JAK & STAT phosphorylation	HTLV-1-T leukemia cells	*Curcuma longa*[2]	curcumin	diarylheptanoid	[72]
► ↑ Caspase-8, ↓ Bcl-XL	Hep G2, Hep 3B	*Justicia procumbens*[7]	justicidin		[73]
► ↑ Caspase-3, ↓ MMP	HL-60	*Curcuma longa*[2]	curcumin	diarylheptanoid	[74]
► ↑ p53 and Bax, ↓ Bcl-2	lung cancer cells	*Ganoderma lucidum*[3]	ganoderic acid T	triterpenoid	[75]
► ↑ Caspase-3 & -8, cleavage of PARP	pancreatic carcinoma PANC-1 & HeLa cells	*Tripterygium wilfordii*[5]	triptolide	diterpene	[76]
► ↑ Caspase-3 & -9, PARP-1	Jurkat T cells	*Albizia julibrissin*[6]	crude extract	NA	[77]
► ↑ Caspase-2 & -3	HL-60	*Oldenlandia diffusa*[1]	crude extract	NA	[78]
► ↑ Caspase-3 & PARP	MCF-7	*Antrodia camphorata*[3]	crude extract	NA	[79]
► ↑ p53, ↓ Bcl-2, ↑ Bax, ↓ NF-kappaB	*in vitro* & *in vivo*	*Artemisia annua L*[1]	artemisinin	sesquiterpene	[31]
► ↓ PI3K/AKT, ↓ FOXO & GSK3 pathways	osteosarcoma cells	*Albatrellus confluens*[7]	grifolin		[80]
► ↑ ROS, ↓ p-Rb, ↓ p27	H HepG2	*Zizyphus jujuba fruit*[3]	organic crude extract		[81]
► ↑ Caspase-3 & PARP	colon cancer cells HT-29		pseudolaric acid B	diterpenoid	[82]
► ↑ Fas-mediated pathway	MCF-7	*Pterocarya stenoptera*[7]	pterocamin A		[83]
► ↑ Caspases	HeLa, A549, HepG2 & SW480	*Cremanthodium humile*[7]	crude extract	NA	[84]
► ↑ Caspase-3, -9, -4. BIP & CHOP (ER)	HL-60		trichosanthin		[85]
► ↑ Caspase-3 & -7	thyroid carcinoma cells	*Stemona tuberosa* Lour[4]	organic fraction	NA	[86]
► ↑ Bax, ↓ Bcl-2, p53-independent	glioma cells	*Tripterygium wilfordii*[5]	triptolide	diterpene	[87]
► ↓ Survivin	lung cancer cells	*Artemisia annua*[1]	dihydroartemisinin	sesquiterpene	[88]
► ↑ Caspase-3 & -9	neuroblastoma	*Angelica keiskei*[7]	isobavachalcone	chalcones	[89]
► not clear	HL-60	*Oroxylum indicum*[1]	baiclein	flavonoid	[90]
► ↑ Bax, ↓ Bcl-2, caspase-8	HL-60	*Garcinia hanburyi*[5]	gambogic acid derivative		[91]
► ↑ PARP cleavage	HepG2	*Schisandra propinqua*[7]	schisandrolic acid	triterpenoid	[92]
► ↑ Caspase-3, cleavage of PARP	HT-29 colon cancer cells	*Astragalus membranaceus*[1]	Astragalus saponins	saponins	[30]
► → Differentiation, GFAP, ↓ nestin	glioma cells	Danshen[2]	tanshinone IIA	phenanthraquinone	[93]
► Caspase-3, PARP& p38, ↓ MAPK	HepG2	*Curcuma wenyujin*[2]	furanodiene		[94]
► ↑ Capspase-like activities	Bcap37	*Trichosanthes kirilowlii*[5]	23,24-dihydrocucurbitancin B		[95]
► ↓ Glutathione, enhance As_2O_3 toxicity	leukemia cells, HL-60	*Isodon melissoides*[7]	melissoidesin G	diterpenoid	[96]
► ↑ p38, ↑ capases-9, -8, -3, -2	leukemia cells	*Aglaia*[7]	rocaglamide	rocaglamide	[97]
► ↑ PLCγ, Ca^{++} overload	T-lymphocytes, *in vitro* & xenograft	*Scutellaria baicalensis*[1]	wogonin	flavenoid	[37]
► Synergize with TRAIL via ↓ XIAP & DR5	AML		triptolide	diterpene	[98]
► via DNA damage & AIF pathway	HCT-116	*Ephemerantha lonchophylla*[3]	denbinobin	phenanthraquinone	[99]

continued next page

Table 1 Examples of anticancer compounds or extracts derived from traditional Chinese herbal medicines with known molecular mechanism of action. *continued*

Affected molecules and pathways	*In vitro* and/or *in vivo* system	Main TCM herbs	Active component*	Type of compound	Ref.
↑ Bax/Bcl-2 ratio, caspase-9, -3, & PARP-1	glioblastoma cells		berberine	isoquinoline alkaloid	[100]
↑ Bax, Bak, & Bad; ↓ Bcl-xL & Mcl-1	prostate PC-3 xenograft	*Magnolia officinalis*[4]	honokiol	lignan	[101]
↓ ERK & MAPK phosphorylation	PC3 prostate cancer cells	*Antrodia camphorata*[3]	crude extract	NA	[102]
↓ Bcl-2	HepG2	*Solanum nigrum* Linn.[1]	solanine	steroid alkaloid	[28]
↑ Caspase-3; ↓ AKT pathway	breast cancer cells	*Cordyceps militaris*[7]	crude extract	NA	[103]
↑ p53 & p21; ↑ caspase-3; ↓ Bcl-2, p-Rb, cdk 2/4 & E2F	uterine leiomyoma cells		isoliquiritigenin	flavonoid	[104]
↑ Caspase-8, -9, -7 & -3; ↑ PARP; ↓ Bcl-xL,	prostate cancer cells DU145	*Saussurea lappa*[6]	dehydrocostus lactone		[105]
↑ Caspase-3, AIF & Bad; ↓ AKT	lung adenocarcinoma A549	*Ephemerantha lonchophylla*[3]	denbinobin		[106]
↑ Caspase-3	pancreatic PANC-1	*Brucea javanica*[1]	Fructus Bruceae		[107]
↑ p53 & p21; caspase-3 & PARP	gastric carcinoma AGS cells	Strychni semen[5]	water extract		[108]
↑ Caspase-3 & -9; PARP	HL-60 cells	*Schizandrae chinensis*[3]	deoxy- & gamma-schizandrin	lignan	[109]
↑ p21, caspase-3 & -9	prostate LNCaP cancer cells	*Stellera chamaejasme* L.[5]	neochamaejasmin A	flavonoid	[110]
↑ Caspases-8, -9, -3; ↓ Bcl-2 & NF-kappaB	oral squamous carcinoma cells		shikonin	naphthoquinone	[111]
↑ Ca^{++} & p38	lung cancer PC-14 cells	*Artemisia annua*[1]	dihydroartemisinin	sesquiterpene	[112]
↓ NF-kappaB pathway via ↓ IκBα kinase (IKK)	jurkat leukemic cells		berberine	isoquinoline alkaloid	[33]
↓ JAK/STAT pathway; ↑ caspase-3, -8 & -9	U266 multiple myeloma cells	*Mylabria phalerata* Pallas (insect)	cantharidin	monoterpene	[113]
↑ Bax; ↓ Bcl-2; stimulate IL-2 & TNF-α	hepatocellular carcinoma HepA cells	*Paeonia moutan*[1]	paeonol	phenolic compound	[38]
↓ IKK kinase activity; ↓ NFkappaB	carcinoma KB cells	*Euphorbia fischeriana*[5]	17-acetoxyjolkinolide B		[114]
↑ Caspase-3 & -9, PARP; ↓ Bcl-2; ↑ Bax	multiple myeloma cells	*Alpinia pricei* Hayata[7]	crude extract	NA	[115]
↓ PI3k/AKT & NF-kappaB; enhance Dex-effectiveness	HeLa	*Tripterygium wilfordii*[5]	triptolide	diterpenoid	[116]
↑ Caspase-3	HCT116 colon cancer cells	*Zingiber zerumbet*[7]	zerumbone		[117]
Enhance 5-FU-induced caspase-6 & apoptosis	gastric carcinoma SCG-7901cells	*Erigeron breviscapus*[1]	scutellarin	flavonoid	[118]
↑ Fas/FasL; caspase-3	oral squamous cell carcinoma	*Sophora flavescens* Ait[1]	matrine	alkaloid	[119]
↑ Caspases, PARP; ↑ ROS	tongue cancer SCC-4 cells	*Anisomeles indica* (L) Kuntze[7]	ovatodiolide	diterpenoid	[120]
↑ Bax/Bcl-2 ratio; ↑ ROS	colon cancer HCT116 cells	rhubarb[2]	rhein	anthraquinone	[121]
Enhance trail-cytotoxicity through ↑ p53 & puma mediated by ROS	breast MDA-MB-453 cancer cells		wogonin	flavonoid	[122]
↓ ErbB-2 pathway; ↑ caspase-3 & PARP; ↑ proapoptotic Bim	MDA-MB-453 breast cancer cells	*Cleistocalyx operculatus*[7]	on-III		[123]
↑ MAG-related mitochondrial pathway	HepG2 liver cancer cells	*Scutellaria baicalensis*[1]	oroxylin A	flavonoid	[124]
↑ Caspase-3	lung adenocarcinoma ASTC cells	*Artemisia annua*[1]	dihydroartemisinin	sesquiterpene	[125]
↑ Bax/Bcl-2 ratio	prostate cancer PC-3 & DU-145 cells & xenograft mouse model	*Lycium barbarum*[3]	polysaccharide fraction	polysaccharides	[126]
↓ Bcl-2; caspase-3; ↑ PARP cleavage	lung carcinoma A549 cells	*Panax notoginseng*[2]	water extract	NA	[127]
↓ TNFα & NF-kappaB; ↑ ROS, caspases	leukemia U937 cells	*Dendrobium moniliforme*[3]	denbinobin	phenanthraquinone	[128]
↑ p21 & p27; ↑ caspase-3 & PARP cleavage	leukemia K562 cells	*Vitex rotundifolia*[1]	casticin		[129]
↑ ROS, Egr-1 & caspase-3	human leukemia U937 cells	*Platycodon grandiflorum*[4]	platycodon D	triterpenoid	[130]
↑ ROS, ↓ MMP, ↓ Bax/Bcl-2 ratio	HT-29 colon cancer cells	*Houttuynia cordata*[1]	crude extract	NA	[131]
↓ Rho GTPases, ↓ metastasis	nasopharyngeal carcinoma, HONE1	*Coptidis rhizoma*	berberine	alkaloid	[132]
↓ IL-6 & JAK/STAT3	prostate LNCap cells	*Euphorbia fischeriana*[5]	17-hydroxyjolkinolide B	diterpenoid	[133]
↑ Bax, ↑ p53, AKT & JNK	TRAMP prostate mouse model & LNCaP cells	*Scutellaria barbata*[1]	crude extract	NA	[134]
↑ Caspase-3, -9; ↑ PARP cleavage; ↓ Bcl-2	ovarian cancer cell iline SKOV3 & *in vivo* SKOV3 xenograft in mice	Rhizoma Paridis[1]	paris saponin 1	saponin	[135]
↑ Caspase-8, -9; ↑ Bax; ↓ Bcl-2	HL-60 cells	*Garcinia hanburyi*[5]	gambogic acid		[136]
↑ Caspase-8, -9; ↑ Bax; ↓ Bcl-2	melanoma A375 cells	*Garcinia hanburyi*[5]	gambogic acid		[137]

continued next page

Table 1 Examples of anticancer compounds or extracts derived from traditional Chinese herbal medicines with known molecular mechanism of action. *continued*

Affected molecules and pathways	*In vitro* and/or *in vivo* system	Main TCM herbs	Active component*	Type of compound	Ref.
▶ ↓ Bcl-2; Fas ligand and receptor	lung carcinoma A549 cells	*Venenum bufonis* (Chansu)[5]	crude extract	NA	[138]
▶ ↓ Bcl-2/Bax ratio; ↑ caspases	macrophage RAW 264.7 & THP-1 cells	*Vitex negundo*[1]	vitexins	lignans	[139]
Others					
▶ ↓ PKA & PKC, ↓ cdc2&CKII	leukimia cells	Chan'su[5]	bufalin	cardiac steroid	[140]
▶ ↓ PKC, ↓ NFkappaB-related transcription from microarray data	breast cancer cells & xenograft	*Coix lachryma jobi* L.[3]	not known	crude emusion	[141]
▶ Induce senescence; ↑ p21 & ↓ p-Rb; ↓ cdc2 & cyclin B1, cell death	RT4, TSGH-8302 & T24 carcinoma	*Antrodia camphorata* (fungi)[3]	crude extract		[29]
▶ Antiangiognesis; ↓ VEGF, VEGFR, MVC			running II		[142]
▶ Stronger than tamoxifen in ER+ & ER− cells	MCF-10A & -7 breast cells	*Salvia miltiorrhiza*[2]	tanshinone IIA	phenanthraquinone	[143]
▶ Cytotoxicity through non-apoptosis mean	ER + MDA-MB-231 & MCF-7 cells	*Leonurus japonicus*[2]	organic extract	NA	[144]
▶ Induce autophagy & autophage-related cell death; ↓ Bcl-2 and mTOR	LNCaP prostate cancer cells	*Glycyrrhiza glabra*[3]	licorice & licochalcone-A		[145]

NA: not applied; ↑: activation; ↓: inhibition; →: induction; * Chemical structures of the active components are shown in **Fig. 3**; # *Aloe vera* (15 g), *Angelica sinensis* (30 g), *Coptis chinensis* (30 g), *Gardenia jasminoides* (30 g), *Gentiana scabra* Bge. (15 g), *Moschus berezovskii* (1.5 g), *Phellodendron amurense* (30 g), *Rheum officinale* Baill (15 g), *Saussurea lappa* (4.5 g), *Scutellaria baicalensis* (30 g); Classification of medicinal herbs based on the properties and actions of Chinese medicinal herbs (see **Table 2** for details): [1] Medicine for heat clearance and detoxification; [2] Medicinal for promoting blood circulation and eliminating stasis; [3] Medicinal for strengthening qi; [4] Medicinal for resolving phlegm and removing stasis; [5] Medicinal with cytotoxic function; [6] Medicinal for dispersing edema and relieving pain; [7] Others

chrome c, followed by the release of cytochrome c and Apaf-1, and activation of caspases-9 and − 3. The caspase-3 then induces degradation of many signaling molecules, including a DNA repair molecule and poly-ADP-ribose polymerase (PARP), and leads to irreversible cell death. The second pathway, the extrinsic receptor-mediated pathway involves death receptors, such as FAS, TNFαR1 & R2, and TrailR. The latter pathway plays a major role in immune responses, but a lesser role in the response to genotoxic stress. As shown in **Table 1**, there are only a small number of TCM-derived compounds that cause apoptosis via the extrinsic pathway. For example, matrine, an alkaloid purified from the Chinese herb *Sophora flavescens* Ait that is known as an anti-inflammation, antifibrotic and anticancer drug from TCM, activates caspase-3 through Fas/FasL in a gastric cancer cell line [34]. Triptolide is a purified component isolated from *Tripterygium wilfordii* that has been effective in treating a variety of inflammatory and autoimmune diseases. Tripolide also shows potent antitumor properties [35]. A study has demonstrated that triptolide not only inhibits XIAP, a potent cellular caspase inhibitor elevated in acute myeloid leukemia (AML) and a factor causing resistance to TNFα-related apoptosis-inducing ligand (TRAIL), but also activates p53 signaling and promotes apoptosis of AMLs. In a separate study [36], tripolide was also found to overcome desmethasone-resistance and to enhance bortezomib/PS-341-induced apoptosis. It is believed that tripolide acts through multiple signaling pathways, including the PI3K/Akt/NF-kappaB observed in human myeloma cells. Wogonin isolated from Huang-Qin (*Scutellaria baicalensis* Georgl.) showed phospholipaseCγ1- and Ca^{++}-dependent apoptosis [37]. Paeonol from the root bark of the TCM herb *Peoinia moutan* is a TCM herb used to activate blood flow and remove blood stasis. Treatment of mice with a series of concentrations of paeonol induced apoptosis of the HepA-xenograft, and meanwhile caused elevation of blood IL-2 and TNF-α in the tumor-bearing mice [38].

Summarizing data from more than 80 independent research papers, it appears that herbal medicines predominately affect apoptotic signaling molecules, including increasing the ratio of Bax/Bcl-2, and upregulating caspases-3, -8, -9 and p53/p21 signals. An intriguing observation is that the elevation of PARP-1 cleavage seems to be a common event in cancer cell lines upon the treatment of TCM drugs. It is known that the inhibition of PARP-1 can potentiate both chemo- and radiotherapies for cancer and therefore the search for inhibitor(s) against PARP-1 has been an active area for the development of anticancer drugs [39]. Conversely, excessive expression of PARP-1 can cause translocation of the mitochondrial apoptosis-inducing factor (AIF) to the nuclei, and cause PARP-1-dependent cell death.

There are few herbs that do not cause apoptosis; instead, these herbs (listed in **Table 1**) generally induce antiangiogenesis, or induce differentiation and change the transforming phenotypes of the tumor cells as listed in **Table 1**. According to the TCM classification of medicinal herbs for cancer treatment, we have classified the herb plants listed in **Table 1** into six major classes and show them in **Table 2**. To sum up the above actions of the TCM-derived herbal compounds and herbal extracts, we have mapped the found molecular targets from **Table 1** to the known cellular signaling network shown in **Fig. 2**. This schematic diagram shows that MAPK/JNK/p38, JAK/STAT, PI3K/AKTS and NF-kappaB are the common signaling pathways affected in responding to the various treatments of TCM. The drawing also illustrates that the caspase family members and the mitochondria-mediated apoptotic molecules might play a role in the anticancer effects of the herbal medicines. However, the information collected up to the time of this review can only offer a rough and incomplete picture of the action of TCM herbal medicines. Further systemic studies are needed for a true and comprehensive understanding of the nature of the TCM products in cancer prevention and treatment.

Table 2 Functional classification of medicinal herbs based on TCM theory and clinical practice.

1. Medicinal for heat-clearance and detoxification (清熱解毒藥)	2. Medicinal for promoting blood circulation and eliminating stasis (活血化瘀藥)	3. Medicinal for strengthening qi (扶正培本藥)	4. Medicinal for resolving phlegm and removing stasis (化痰散結藥)	5. Medicinal with cytotoxic function (以毒攻毒類藥)	6. Medicinal for dispersing edema and relieving pain (消腫止痛藥)	7. Others (其他藥)
Artemisia annua L. 黃花蒿	*Curcuma longa* 薑黃	*Antrodia camphorata* 牛樟芝*	*Alismatis rhizoma* 澤瀉	*Bufo bufo gargarizans*/	*Albizia julibrissin* 合歡	*Aglaia* 米仔蘭*
Astragalus membranaceus 黃芪	*Curcuma wenyujin* 温鬱金	*Coix lacryma-jobi* L. (Coix seeds) 薏苡仁	*Magnolia officinalis* 厚樸	*Bufo melanostictus* (*Venenum bufonis*/Chan'su) 蟾酥	*Saussurea lappa* 木香*	*Albatrellus confluens**
Brucea javanica 鴉胆子	*Curcuma xanthorrhiza* 束骨薑黃*	*Coriolus versicolor* 彩絨革蓋菌(雲芝)	*Platycodon grandiflorum* 桔梗	*Camptotheca acuminata* 喜樹*		*Alpinia pricei* Hayata 普萊氏月桃*
Coptidis Rhizoma (*Coptis* species)黃連	*Leonurus japonicus* 益母草	*Dendrobium moniliforme* 白石斛*	*Stemona tuberosa* Lour 百部	*Daphne genkwa* 芫花		*Angelica keiskei* 明日葉*
Erigeron breviscapus 燈盞細辛	*Panax notoginseng* 三七	*Ephemerantha lonchophylla* 大爪石斛*	*Trichosanthes kirilowii* 栝蔞	*Euphorbia fischeriana*/(*Stellera chamaejasme* L.*)狼毒		*Anisomeles indica* (L) Kuntze 金劍草*
Houttuynia cordata 魚腥草	*Rheum officinale* Baill (*R. palmatum*) (rhubarb)大黃	*Glycyrrhiza glabra* 甘草	*Vitex negundo* 牡荊	*Garcinia hanburyi* 藤黃*		*Cleistocalyx operculatus* 水翁*
Oldenlandia diffusa 白花蛇舌草	*Salvia miltiorrhiza* Bge. (Danshen) 丹參	*Ganoderma lucidum* 赤芝		*Strychnos nux-vomica* (Strychni semen) 馬錢子		*Cordyceps militaris* 蛹蟲草*
Oroxylum indicum 木蝴蝶		*Lycium barbarum* 寧夏枸杞		*Tripterygium wilfordii* 雷公藤*		*Cremanthodium humile* 矮垂頭菊*
Paeonia suffruticosa (*Paeonia moutan*) 牡丹皮		*Poria cocos* 茯苓				*Inonotus obliquus* Pilat 白樺茸*
Paris polyphylla (Rhizoma Paridis) 七葉一枝花		*Schisandra chinensis* 五味子				*Isodon melissoides**
Patrinia scabiosaefolia 黃花敗醬**		*Zizyphus jujuba* fruit 大棗				*Justicia procumbens* 爵床*
Rabdosia rubescens 冬凌草						*Pterocarya stenoptera* 楓楊*
Scutellaria baicalensis 黃芩						*Schisandra propinqua* 香巴戟*
Scutellaria barbata 半枝蓮						*Sophora moorcroftiana* 砂生槐*
Solanum nigrum Linn 龍葵**						*Zingiber zerumbet* 紅球薑*
Sophora flavescens Ait. (Kushen) 苦參						
Vitex rotundifolia 蔓荊*						

* Drugs not included in "China Pharmacopia, 2010"; ** Medicinal included in the Appendix of "China Pharmacopia, 2010"; () Different species name under the same TCM name

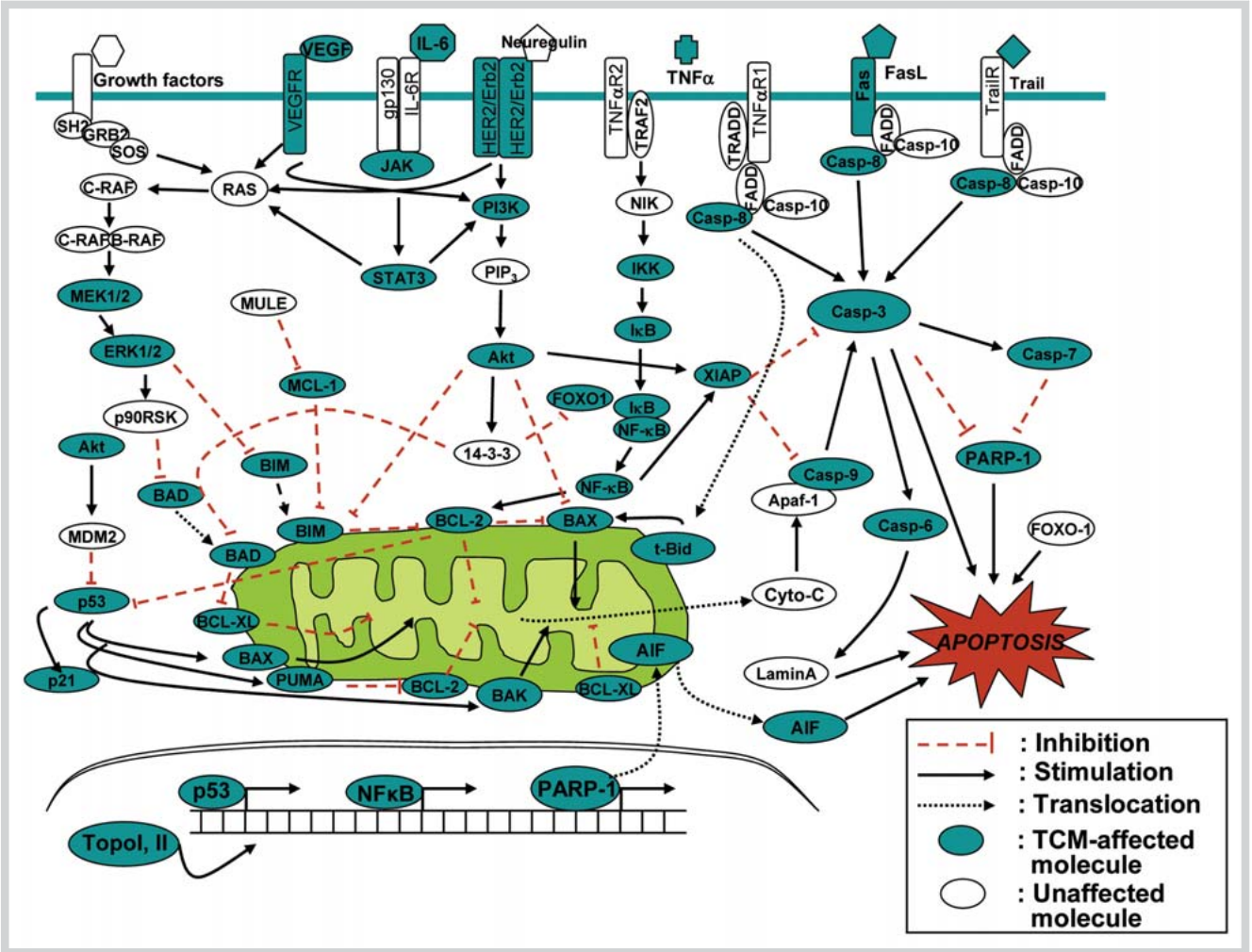

Fig. 2 The altered protein molecules (shown in ◉ **Table 1**) upon treatments of TCM herbal medicines and the associated cellular signaling networks.

Anticancer Effects and Underlying Mechanisms of TCM-Derived Complex Formulas

There are only a few mechanistic studies on the action of TCM formulas as anticancer agents. One study was on San-Zhong-Kui-Jian-Tang (SZKJT) [40], a complex formula comprising 17 different herbs, that is used for cancer therapy in China. SZKJT was found to induce the mitochondrial apoptotic pathway by changing Bax/Bcl-2 ratios, cytochrome c release and caspase-9 activation, but did not act on Fas/Fas ligand pathways in two human breast cancer cell lines, MCF-7 and MDA-MB-231. A similar study was carried out by the same laboratory [41] on huang-lian-jie-du-tang (HLJDT) known to possess anti-inflammatory activity. The *in vitro* study conducted in two human liver cancer cell lines, HepG2 and PLC/PRF/5, found that HLJDT caused cell arrest by up-regulating the inactive form of Cdc2 and Cdc25, and downregulating the levels of Bcl-2 and Bcl-XL. Furthermore, HLJDT increased the ratio of Bax and Bak/Bcl-2 and Bcl-XL and the associated cell survival pathways, and subsequently triggered the mitochondrial apoptotic pathway. It was the collective actions of the herbs in the formula that were inhibiting the growth of cancer cells tested both *in vitro* cell lines and *in vivo* in nude mice. Another study is the study of a classic formula, Guizhi-fuling decoction (GZFLD) [42]. The formulation consists of five herbs: *Cinnamomum cassia, Paeonia lactiflora, Paeonia suffruticosa, Poria cocos*, and *Prunus persica*. Accordingly, GZFLD inhibited the growth of HeLa cells by activating the tissue inhibitor of metallopeptidases (TIMPs) and causing the suppression of the activity of the matrix metallopeptidase (MMPs) that play a key role in the degradation of the extracellular matrix and promotion of cell proliferation. In the same study, GZFLD was also shown to inhibit tumor growth and angiogenesis in an *in vivo* animal model. Another report [43] concerned a classic formula "bojungbangdocktang (BJBDT)" consisting of *Astragalus membranaceus* Bunge, *Atractylodes japonica* Koidzumi, *Coiz lacryma-jobi* Linne var. ma-yuen stapf, *Dioscorea batatas* Decaisne, *Dolichos lablab* Linne, *Panax ginseng* C. A. Mey, *Polygonatum sibiricum* Delar. ex Pedouté, *Poria cocos* (Schw.) Wolf. Two related studies [44,45] found that BJBDT demonstrated antiangiogenesis by blocking VEGF/VEGFR activities in human umbilical vein endothelial cells. Interestingly, BJBDT can prevent cisplatin-induced toxicity and apoptosis in normal MCF-10A, but not in MCF-7 and MDA MB-231 breast cancer cells, suggesting the herbal formula can be applied as a cancer chemopreventive agent [43]. The synergistic effects of herbs in a TCM formula were well illustrated in a recent study, in which a TCM-based formula, Realgar-indigo naturalis (RIF), was applied in the treatment of acute promyelocytic leukemia (APL). The RIF formula has three components, realgar, indigo naturalis, and *Sal-*

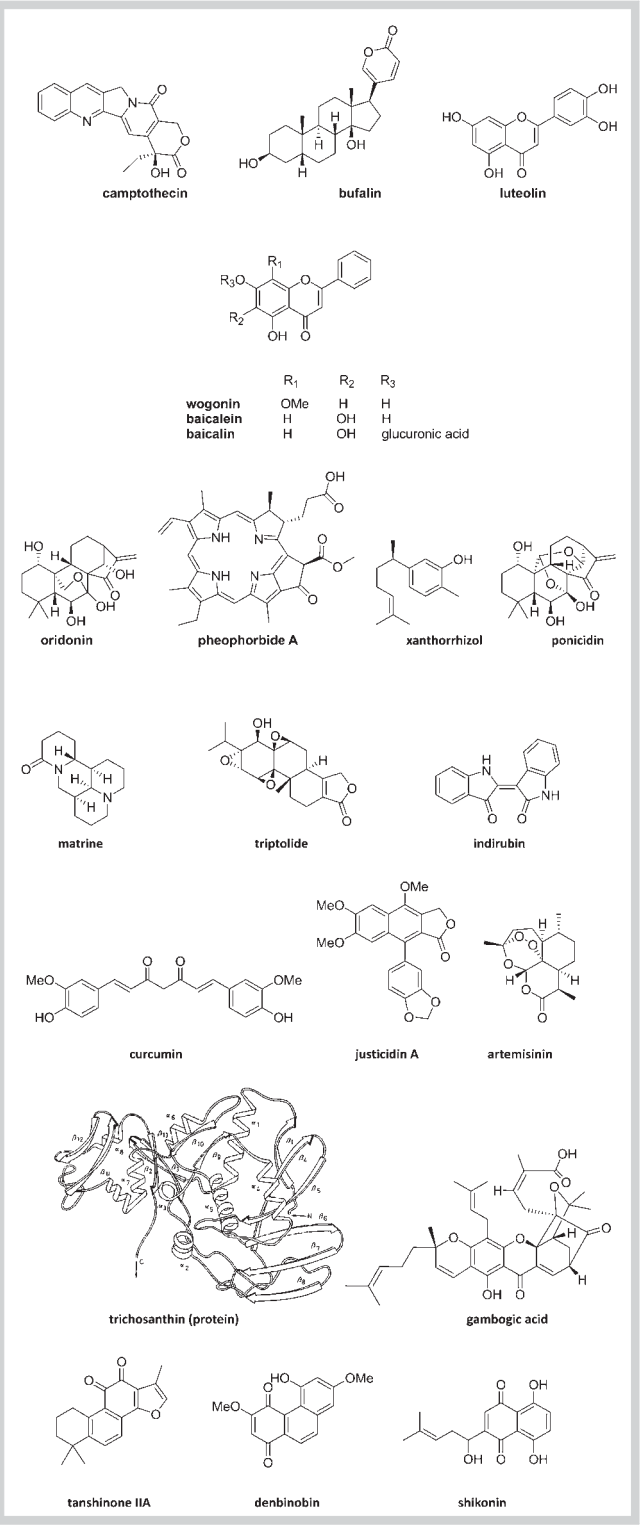

Fig. 3 Chemical structures of the TCM-derived active components shown in ◉ **Table 1**.

via miltiorrhiza of which tetra-arsenic tetrasulfide, indirubin, and tanshinone IIA, respectively, are the major active ingredients [46]. The study demonstrated that tetraarsenic tetrasulfide is the principle component of the formula, while tanshinone IIA and indirubin are the adjuvant ingredients. Together these herbs have shown a synergistic action against APL effective in both *in vitro* and clinical studies.

Future Prospect of TCM Herbal Medicines in Cancer Research

The cellular and animal studies have provided strong molecular evidences for the anticancer activities of the TCM herbal medicines, tested as pure compounds or as crude extracts of the single herbs or the complex formulas. However, several important questions remain to be answered. Do TCM-derived herbal medicines possess any special effects other than those often seen with conventional drugs for cancer treatment? There has been little investigation to make a side-by-side comparison. An earlier work was conducted on the anticancer effects of protodioscine (glycosides) from the rhizome of *Dioscorea collettii* var. *hypoglauca*, a Chinese herbal remedy for the treatment of cervical carcinoma, carcinoma of urinary bladder and renal tumor for centuries, against a 60 NCI human cancer panel [47], and it was found to be specifically effective for cervical carcinoma, bladder and renal cancer cell lines. Moreover, based on an analysis of the COMPARE computer program with protodioscin as a seed compound, no other compounds in the NCI's anticancer drug screen database have a cytotoxicity pattern (mean graphs) similar to those of protodioscin, indicating that a potential novel mechanism of anticancer action is involved. This may be one of many methods by which the unique properties of TCM can be revealed in a concise manner.

The other question to be addressed in the future is whether the methodologies and the *in vitro* and *in vivo* biological models currently employed to investigate the therapeutic nature of traditional Chinese medicines are good enough. In this review, there are 66 herbs that have been used for anticancer studies. We have grouped these herbal plants into seven functional groups based on the traditional usage for cancer treatment (◉ **Table 2**). Interestingly only a small subset of herbs is considered toxic, grouped under the category of "medicinal with cytotoxic function", the majority is not. On the other hand, the majority of TCM-derived components shown above are in the same category as the conventional anticancer drugs which induce apoptosis. In a previous study [48], we used a cell system by which the inhibitory effects of non-cytotoxic chemicals were assessed by a focus formation assay upon transfection of *ras* oncogene to the host cells. Using this system, two well-studied medicinal mushrooms *Ganoderma lucidum* and *Tricholoma lobayense* with anticancer potential were examined for their possible adverse effects on cell transformation induced by *ras* oncogene. The results indicated that both species of mushrooms strongly inhibited *ras*-induced cell transformation. However, the inhibitory effect of the mushroom extracts was not due to a direct killing of the transformed cells; rather, it seems to have been mediated through the surrounding normal cells. This normal cell-dependent growth inhibitory effect is also observed with oleanolic acid isolated from *Oldenlandia diffusa* [49]. These examples suggest that, at least some, TCM medicines exert their anticancer effects through mechanism(s) other than apoptosis.

Looking forward, we see three specific issues that will require focused attention: (i) more well-designed clinical trials are required to support the effectiveness and the safety of TCM in the management of cancers; (ii) new parameters based on the unique properties and theory of TCM are needed to assess the clinical ef-

ficacy of TCM in clinical trials; and (iii) new approaches to research may be needed, given the nature of TCM herbs as being fundamentally different from drugs. There is evidence that the reductionist approach, i.e., searching for one or a few active ingredients in an herb or formula, may not elucidate the efficacy of herbal medicines; a systems biology approach may be more appropriate and productive, in terms of developing effective treatment protocols.

Undoubtedly, the evaluation of the therapeutic effects and the benefits of TCM therapy for cancer patients is a significantly complex, albeit significant, issue. TCM therapy, based on multiple medicinal herbs and an holistic approach to diagnosis as well as treatment, means that a clinical study of TCM treatment is more difficult and complicated than the study of single compound drugs. In addition to the conventional "standards" used for WM clinical trail, there is a need to develop a set of parameters that are suitable to the assessment of TCM therapy. The effects, as well as the toxicity, of individual herbs or, especially, of single compounds derived from the herb cannot completely reflect the benefits and toxicity of the herbal combination. When whole herbs are not studied, improper or biased results and conclusions might be unavoidable [50]. As a goal, to develop TCM into rational cancer therapy, more well-designed intensive clinical evaluations and translational laboratory studies are absolutely needed. And, close collaboration between TCM and conventional Western medicine professions and a combination of TCM with modern multidisciplinary cutting-edge technologies, such as omic methodology on systems biology [51], would provide us with an attractive and effective strategy to achieve this goal.

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