INTRODUCTION

Herbal remedies have been used in the treatment of cancer for thousands of years in numerous countries, including China, Egypt, and Japan. Some have come to be accepted as forms of complementary and alternative medicines in Western countries. Many anticancer drugs, such as paclitaxel, arsenic trioxide (As$_2$O$_3$), and Camptothecin (CPT), were derived from natural compounds. With a new understanding of the molecular mechanisms of tumorigenesis, researchers are able to explain some of the anticancer mechanisms of chemotherapeutics. For instance, Paclitaxel interferes with the normal breakdown of microtubules during cell division. CPT binds to topoisomerase I and the DNA complex and prevents DNA relegation, therefore causing DNA damage that results in apoptosis.

However, unlike Western medicines, which generally consist of purified compounds, traditional Chinese medicine (TCM) may comprise multiple herbs and components acting simultaneously on multiple cellular mechanisms and molecular targets. In addition, there are more and more chemicals with strong anticancer activities being discovered in natural products. Therefore, the mechanisms of action (MOA) of many compounds and TCMs are unclear, which makes it difficult to develop them as anticancer drugs. It is necessary to summarize the achievements of TCM in anticancer research to give researchers some guidance and review potential applications. In some recent reviews, scientists summarized progress in certain aspects, including the analysis of the antitumor properties of natural compounds and TCMs, the effects of TCM as adjuvant treatment during chemo- or radio-therapy, the application of proteomics to study the mechanisms of TCM, and the molecular and cellular mechanisms of TCM in cell death pathways. In this review, we focus on the MOA of single compounds or TCM recipes in combination with clinical therapeutics and provide information on specific cancer types. We hope that this review will benefit researchers who are working with TCM in preclinical and clinical studies.

Keywords: Anticancer, interactions, natural compounds, traditional Chinese medicine, traditional Chinese medicine formulae
The mechanisms associated with these TCMs are summarized in Table 1.

**Single Compounds Combined with Anticancer Drugs**

Many natural compounds exhibit strong anticancer activities against multiple cancer cells. However, the therapeutic effects of these compounds normally are not comparable to that of clinical anticancer drugs. In addition, it is difficult to elucidate the MOA of the TCM due to the complex constituents of the herbal medicine. Isolating single compounds from plants and investigating the MOA of them was proved to be an efficient strategy to develop lead compounds. Compared to chemotherapeutics, the natural compounds always activated multiple signaling pathways on cancer cells. When combined with clinical drugs, the compounds exhibited synergetic effects on cell death, cell cycle arrest, drug resistance, metastasis, etc. Therefore, investigating the effects of natural compounds and clinical drugs in combination is a promising strategy. We summarized the studies focusing on the different MOAs of single compounds in this section.

**Compounds target cell death and cell cycle**

Su et al. showed that gambogenic acid (GNA) enhanced the effects of 5-fluorouracil (5-FU) on lung cancer cells by triggering both apoptosis and necrosis. Multiple proteins, such as caspases, bax, RIP1, apoptosis-inducing factor, voltage-dependent anion channel, and cyclophilin D, were carefully examined in that study and the authors revealed that GNA had a profound impact on lung cancer cells when combined with 5-FU.[13] In addition, other effective compounds, including xanthones, benzophenones, and polycyclic polyprenylated acylphloroglucinols (PPAPs) isolated from *Garcinia* species, had strong anticancer efficacy.[14] Our study indicated that Guttiferone K, a PPAP isolated from *Garcinia cowa* Roxb, inhibited colon cancer proliferation by p21/Waf1/Cip1-mediated G0/G1 cell cycle arrest and apoptosis *in vitro* and *in vivo*. We showed that Guttiferone K significantly decreased tumor volumes in a syngeneic colon tumor model with 5-FU without significant toxicity to the animals.[15] Interestingly, another compound, oblongifolin C, extracted from *Garcinia yunnanensis* Hu, had a strong autophagic flux inhibitory effect by inhibiting autophagosome-lysosome fusion, resulting in synergetic effects when combined with a calorie-restrictive diet in a xenograft cervical tumor model.[14] Similarly, Guttiferone F, a prenylated benzophenone isolated from *Garcinia esculenta*, acted on prostate cancer, while caloric restriction significantly enhanced its effect in a mouse model.[19]

Matrine is a compound obtained from Leguminosae, such as *Sophora flavescens* Ait, with anticancer activity arising from apoptotic induction and cell cycle arrest. As₂O₃, discovered from TCM, has been used for treating acute promyelocytic leukemia. When combined together, As₂O₃ exhibited synergetic effects with matrine on RPMI8226 and U266 cells by activating apoptosis through the activation of caspase-3 and PARP, upregulation of Bim, and downregulation of Bcl-2 and phosphor-Akt.[45]

Triptolide, a compound extracted from the root of *Tripterygium wilfordii*, has been shown to have bioactivities against various diseases such as cancer and rheumatoid arthritis.[46] Multiple research groups have investigated the synergetic effects of triptolide with several anticancer drugs. For instance, Lin et al., found that a triptolide and vasostatin 120–180 combination treatment caused the activation of pro-apoptotic proteins and the suppression of nuclear factor (NF)-κB transcription, resulting in a higher efficacy *in vitro* and *in vivo*.[20] Similarly, in gastric cancer cells, the combination of triptolide and cisplatin enhanced the activation of mitochondrial apoptotic pathways *in vitro* and *in vivo*.[21] In another study, Liu et al. showed that triptolide enhanced the anticancer activity of oxaliplatin in colon cancer partially through inhibiting the nuclear translocation of β-catenin and the expression of its target genes.[23] Triptolide also can be co-treated with TRAIL to increase its apoptotic induction ability in pancreatic cancer cells.[23]

Celastrol is an active anticancer compound identified from Thunder of God Vine Root extracts, and its molecular mechanisms and protein targets were widely studied.[47] Celastrol was found to have synergistic effects with many anticancer drugs against various cancers. Yang’s group extensively explored the functional role of celastrol combined with conventional chemotherapeutics in several cancers. First, they found that the combination of TRAIL/APO-2 L and celastrol exerts a strong synergistic antiproliferative effect against cancer cells, including cell lines such as ovary cancer OVCAR-8, colon cancer SW620, and lung cancer 95-D, by prompting caspase-mediated apoptosis.[54] In a follow-up study, they further elucidated that the drug synergisms were largely dependent on the upregulation of death receptor 4 (DR4) and DR5 expression at the mRNA, total protein, and cell surface levels in ovarian carcinoma and colorectal carcinoma.[25] Second, in hepatocellular carcinoma cells, celastrol triggered endoplasmic reticulum stress with NOXA in an elf2α-ATF4 dispensable manner, resulting in enhancing the apoptotic effect of a BH3 mimic, ABT-737.[26] Third, their recent report showed that the combination of celastrol and SAHA (suberoylanilide hydroxamic acid, an histone deacetylase inhibitor) exerted synergistic efficacy against human lung cancer, which was mainly caused by NF-κB inhibition and E-cadherin upregulation.[27] Maysinger’s group studied the effect of celastrol with an HSP90 inhibitor in glioblastoma cells. They provided evidence that the celastrol-induced cell death was mainly through the induction of proteotoxic stress, which involved the impairment of protein quality control and the induction of the heat shock proteins HSP72 and HSP90.[48] Curcumin, the major polyphenolic curcuminoid extracted from the turmeric rhizome *Curcuma longa*, has been widely studied for its potential chemopreventive and chemotherapeutic
### Table 1: Summary of synergetic effects of traditional Chinese medicines with anticancer drug

<table>
<thead>
<tr>
<th>Chemicals</th>
<th>Clinical drugs</th>
<th>Cancer types</th>
<th>Mechanism of action</th>
<th>References</th>
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<tbody>
<tr>
<td><strong>Single compounds</strong></td>
<td></td>
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<tr>
<td>Curcumin</td>
<td>Mitomycin C; docetaxel</td>
<td>Breast cancer; lung cancer</td>
<td>Induces cell cycle arrest by inhibiting cyclin D1, cyclin E, cyclin A, CDK2, and CDK4; reduces toxicity to bone marrow and liver in vivo</td>
<td>[6,7]</td>
</tr>
<tr>
<td>Baicalein</td>
<td>Doxorubicin</td>
<td>Breast cancer</td>
<td>Combined with nanostructure lipid carriers to increase cytotoxicity</td>
<td>[8]</td>
</tr>
<tr>
<td>Celastrol</td>
<td>TRAIL/APO-2L; ABT-737; SAHA; HSP90 inhibitor</td>
<td>Ovarian carcinoma; colorectal carcinoma; hepatocellular carcinoma; lung cancer; and glioblastoma</td>
<td>Induces apoptosis upregulation of DR4 and DR5, induces apoptosis through activating ER stress and NOXA, induces apoptosis through NF-kB inhibition and E-cadherin upregulation, and induces proteotoxic stress</td>
<td>[9-12]</td>
</tr>
<tr>
<td>Gambogenic acid</td>
<td>Doxorubicin; 5-FU</td>
<td>Breast cancer; lung cancer; and ovarian cancer</td>
<td>Sensitizes drug-resistant cells through inhibiting P-gp and survivin; triggers both apoptosis and necrosis via ROS and mitochondrial pathways</td>
<td>[13-15]</td>
</tr>
<tr>
<td>Genistein</td>
<td>Gemcitabine; erlotinib; 5-FU</td>
<td>Pancreatic cancer</td>
<td>Inhibits NF-kB and Akt activation; induces apoptosis and autophagy</td>
<td>[16-18]</td>
</tr>
<tr>
<td>Guttiferone K</td>
<td>5-FU</td>
<td>Colon cancer</td>
<td>Induces G0/G1 cell cycle arrest and apoptosis by activating p21/Waf1/Cip1</td>
<td>[19]</td>
</tr>
<tr>
<td>NCTD</td>
<td>ABT-263; ABT-737</td>
<td>Neuroblastoma; hepatocellular carcinoma</td>
<td>Activates apoptosis through upregulation of NOXA; represses Mcl-1 mRNA level</td>
<td>[20,21]</td>
</tr>
<tr>
<td>Matrine</td>
<td>Arsenic trioxide</td>
<td>Myeloma cells</td>
<td>Activates apoptosis through activation of caspase-3 and PARP, upregulation of Bim, downregulation of Bcl-2 and phosphor-Akt</td>
<td>[22]</td>
</tr>
<tr>
<td>Berberine</td>
<td>2-deoxy-D-glucose</td>
<td>Breast cancer; colon cancer</td>
<td>ATP energy depletion and disruption of UPR</td>
<td>[23]</td>
</tr>
<tr>
<td>Triptolide</td>
<td>Vasostatin 120-180; oxaliplatin; Cisplatin; TRAIL</td>
<td>Lung cancer; colon cancer; gastric cancer; pancreatic cancer</td>
<td>Activates apoptosis through upregulation of caspases, Bax, Bak, and Bad suppression of NF-kB; activates apoptosis through inhibiting nuclear translocation of β-catenin; activates apoptosis through mitochondrial pathways; activates apoptosis</td>
<td>[24-27]</td>
</tr>
<tr>
<td>Cinnamaldehyde</td>
<td>Oxaliplatin, 5-FU</td>
<td>Colorectal carcinoma</td>
<td>Activates apoptosis through regulating drug-metabolizing genes</td>
<td>[28]</td>
</tr>
<tr>
<td>Bufalin</td>
<td>5-FU; topotecan; camptothecin; etoposide; vinorestat</td>
<td>Hepatocellular carcinoma; multiple myeloma cells</td>
<td>Activates apoptosis and reduces drug resistance; inhibits PARP1 activity</td>
<td>[29,30]</td>
</tr>
<tr>
<td>Honokiol</td>
<td>Ionizing radiation</td>
<td>Colon cancer; cancer stem cells</td>
<td>Inhibits notch signaling pathway and DCLK1</td>
<td>[31]</td>
</tr>
<tr>
<td>β-elemene</td>
<td>Cisplatin; etoposide</td>
<td>Lung cancer</td>
<td>Activates apoptosis through Bcl-2 family proteins; activates apoptosis through p53 and p21</td>
<td>[32,33]</td>
</tr>
<tr>
<td>Crocin</td>
<td>Cisplatin</td>
<td>Osteosarcoma</td>
<td>Inhibits invasion and activates apoptosis</td>
<td>[34]</td>
</tr>
<tr>
<td><strong>Traditional Chinese medicine extracts and formula</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>PHY906</td>
<td>CPT-11</td>
<td>Colon cancer</td>
<td>Inhibits inflammation and promotes progenitor cell repopulation</td>
<td>[35]</td>
</tr>
<tr>
<td>Yang Zheng Xiaoji</td>
<td>Cyclopamine</td>
<td>Nonsmall cell lung cancer</td>
<td>Sonic hedgehog, EMT</td>
<td>[36]</td>
</tr>
<tr>
<td>FWGE</td>
<td>Cisplatin, docetaxel, 5-FU</td>
<td>Ovarian carcinoma cells; hepatocellular carcinoma</td>
<td>Increases apoptosis and cytotoxicity through caspase-3 and caspase-7</td>
<td>[37,38]</td>
</tr>
<tr>
<td>TLBZT</td>
<td>5-FU</td>
<td>Colon carcinoma</td>
<td>Activates apoptosis, induces senescence, inhibits angiogenesis</td>
<td>[39]</td>
</tr>
<tr>
<td>ZJW</td>
<td>L-OHP; DDP; 5-FU; mitomycin</td>
<td>Colorectal cancer</td>
<td>Reverses drug resistance by decreasing P-gp level</td>
<td>[40]</td>
</tr>
<tr>
<td>Fuzheng-Yiliu granules</td>
<td>5-FU</td>
<td>Hepatoma</td>
<td>Induces apoptosis and increases white blood cell and lymphocyte</td>
<td>[41]</td>
</tr>
</tbody>
</table>

Contd...
activities against various cancers. The administration of curcumin with other chemotherapy drugs also contributed a significant benefit in preclinical studies. For instance, curcumin increased cell cycle G1 arrest with mitomycin C in MCF7 lung cancer cells in vitro and in vivo by inhibiting cyclins (e.g., cyclin D1, cyclin E, and cyclin A) and CDK2, and activating p21 and p27.[49] In addition, curcumin exhibited synergetic efficiency with docetaxel in lung cancer.

Genistein, an isoflavone extracted from soybeans, was found to inhibit cell proliferation, apoptosis, and angiogenesis, especially in pancreatic cancer cells.[9] Several preclinical studies indicated that genistein could inhibit the activation of the Akt and NF-κB signaling pathways and increase the chemotherapy efficacy of first-line drugs, including gemcitabine and erlotinib.[10,11] In a recent report, genistein was shown to induce cell death through apoptosis and autophagy when combined with 5-FU.[12] With the promising preclinical data, the combination of genistein, gemcitabine, and erlotinib has been approved to undergo clinical study. Although one Phase II study reported that this combination was not of benefit in late‑stage pancreatic cancer patients, it does not rule out the possibility that genistein is a potential drug for other pancreatic cancers.[9]

Cinnamaldehyde is an active compound isolated from the stem bark of *Cinnamomum cassia*, which possesses marked antitumor effects against multiple cancer cells. In colorectal carcinoma, cinnamaldehyde showed synergetic effects with 5-FU and oxaliplatin by suppressing some drug-metabolizing genes, including excision repair cross-complementing 1, orotate phosphoribosyltransferase, thymidylate synthase (TS), breast cancer susceptibility gene 1, and topoisomerase 1.[7]

Honokiol is a biphenolic compound from *Magnolia officinalis* and is used for the treatment of various ailments, including cancer. The honokiol-ionizing radiation (IR) combination suppressed proliferation and colony formation with the induction of apoptosis in colon cancer cells. Specifically, this combination reduced spheroid number and size, suggesting that the cancer stem cells were killed. The mechanistic study indicated that the suppression of the Notch signaling pathway and the colon cancer stem cells marker DCLK1 were the targets of Honokiol.[50]

<table>
<thead>
<tr>
<th>Chemicals</th>
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<th>Mechanism of action</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>CF</td>
<td>Cisplatin</td>
<td>Nonsmall cell lung cancer</td>
<td>G0/G1 cell cycle arrest by inhibiting cyclin D1, PCNA, and Rb</td>
<td>[42]</td>
</tr>
<tr>
<td>Kangluzengxiao decoction; Feiyanning decoction</td>
<td>Navelbine; cisplatin</td>
<td>Lung cancer</td>
<td>Clinical study</td>
<td>[43]</td>
</tr>
</tbody>
</table>

The combination of β-ELE, extracts from *Curcuma zedoaria*, and cisplatin enhanced apoptosis by upregulating pro-apoptotic proteins (e.g., cytochrome c, Bad) and downregulating anti-apoptotic proteins (e.g., Bel-2). In that study, β-ELE effectively reversed the drug resistance of cisplatin in lung cancer cells.[51] In an earlier study, Zhang et al. revealed that a β-ELE and etoposide combination also enhanced the apoptotic induction effect in nonsmall cell lung cancer cells, mainly through activating the p53 and p21 signaling pathways.[52]

**Comounds attenuate drug resistance**

Gambogic acid (GA) was shown to markedly sensitize doxorubicin (DOX)-resistant breast cancer cells by inhibiting both P-glycoprotein (P-gp) and survivin expression. A mechanistic study indicated that ROS-mediated p38 MAPK was involved in the synergetic effect.[53] A similar synergetic effect and mechanism were also observed in ovarian cancer cells.[16]

Norcantharidin (NCTD) is a small molecule derived from the TCM blister beetle. Liu’s group reported that NCTD could overcome the resistance to ABT-737 in hepatocellular cancer cell lines, as well as the resistance to ABT-263 in neuroblastoma cells. These studies suggested that NCTD triggered apoptosis by different mechanisms, including upregulating NOXA and repressing the Mcl-1 mRNA level.[17,18]

Two studies reported that curcumin had a strong synergetic effect with gemcitabine in pancreatic adenocarcinoma.[8,54] Although the detailed mechanisms are still under investigation, curcumin is in clinical trials and the current results suggest its promising application when administered with gemcitabine in gemcitabine-resistant pancreatic cancer patients.[34]

Bufalin, bufotalin, telocinobufagin, and cinobufagin are the main bufadienolides extracted from *Venenum Bufonis*. Among these compounds, bufalin exhibits antitumor activities against several types of cancer cells.[55] Several studies suggested that bufalin could enhance the antitumor activities of clinical drugs by different mechanisms. In BEL-7402 multidrug-resistant (MDR) cells, bufalin efficiently suppressed MDR-related genes, including TS, P-gp, and MDR protein 1, resulting in a synergetic effect with 5-FU treatment.[29] In addition, Wu’s study indicated that bufalin was an effective PARP1 inhibitor and was able to enhance the efficacy of
several drugs (e.g., topotecan, CPT, etoposide, and vorinostat) on multiple myeloma cells.[30]

**Compounds act on other signaling pathways**

Berberine (BBR) is an isoquinoline derivative alkaloid isolated from many medicinal herbs and is widely used for the treatment of many diseases, including cancer. 2-deoxy-D-glucose (2-DG) is an effective inhibitor of glucose metabolism by targeting hexokinase and has been demonstrated to have anticancer potential in both preclinical and clinical studies. In lung and colon cancer cells, the combination of these two chemicals resulted in a dramatic growth inhibition. Interestingly, a mechanistic study suggested that BBR and 2-DG enhanced ATP depletion and disrupted the unfolded protein response.[28]

Curcumin reduced the cytotoxicity to docetaxel against bone marrow and liver, though the detailed mechanism was not elucidated, suggesting that curcumin might have a systematic effect regulating anticancer activity in animals.[31]

Liu et al. used hyaluronic acid lipid to co-deliver baicalein and DOX and reported a synergetic effect in breast cancer therapy *in vitro and in vivo*; however, the detailed mechanism is not understood.[32] Crocin, an active compound isolated from saffron, could suppress invasion and induce apoptosis in osteosarcoma cells when combined with cisplatin.[33]

**Traditional Chinese Medicine Extracts and Formulae Combined with Anticancer Drugs**

It is much more difficult to elucidate the MOA of TCM formulae because they contain many active compounds and target multiple signaling pathways.

Prof. Cheng’s group devoted a large effort to study the effect of PHY906, an 1800-year-old Chinese medicine formula, on gastrointestinal cancer.[56] PHY906, consisting of four herbs (Glycyrrhiza uralensis Fisch, Paeonia lactiflora Pall, Scutellaria baicalensis Georgi, and Ziziphus jujuba Mill [Z]), is traditionally used for treating different gastrointestinal symptoms, including diarrhea, nausea, and vomiting. Cheng’s group began using a murine model to investigate the protective effects of CPT-11 on the intestinal system. PHY906 reduced the gastrointestinal toxicity of CPT-11 through inhibiting inflammation and promoting intestinal progenitor cell repopulation. The inflammatory inhibition occurs mainly through downregulating the NF-κB-mediated transcriptional activity and COX-2 and iNOS enzyme activity, possibly contributed by the flavonoids. In addition, PHY906 potentiated the Wnt-signaling pathway and caused the repopulation of crypt cells.[35] In a later study, they performed a gene expression microarray to analyze the effects of PHY906 with or without CPT-11 in tumors, spleen, and liver. Interestingly, the evidence suggested that PHY906 and CPT-11 together could induce pro-inflammatory and pro-apoptotic effects in tumors, but not in other tissues, such as liver and spleen. They concluded that PHY906 could enhance the therapeutic window for CPT-11 as it could decrease toxicity in normal tissues while promoting cell death within the tumor.[57]

When combined with the Sonic Hedgehog (SHH) inhibitor cyclopamine, the TCM formula YangZheng XiaoJi showed a profound inhibitory effect on lung cancer metastasis. The authors suggested that YangZheng XiaoJi might regulate multiple pathways, including SHH and epithelial-to-mesenchymal transition and the reduction of drug resistance.[38]

Fermented wheat germ extract (FWGE) is a nutrient supplement with potential anti-ovarian activity. Wang et al. provided *in vitro* data to show that FWGE could enhance the efficacy of cisplatin and docetaxel against SKOV-3 and ES-2 cells through activating caspase-3 and caspase-7, respectively.[36] They also provided evidence that FWGE enhanced the effect of cisplatin and 5-FU in hepatocellular carcinoma through similar mechanisms.[37]

The combination of β-ELE, extracts from *Curcuma zedoaria*, and cisplatin enhanced apoptosis by upregulating pro-apoptotic proteins (e.g., cytochrome c, Bad) and downregulating anti-apoptotic proteins (e.g., Bcl-2). In this study, β-ELE effectively reversed drug resistance to cisplatin in lung cancer cells.[51]

Teng-Long-Bu-Zhong-Tang (TLBZT) consists of eight herbs, including Actinidia chinensis, Solanum nigrum, Duchesnea indica, Atractylodes macrocephala Koidz, Potia cocos, Coix seed, Mistletoe and Scutellaria barbata. TLBZT significantly enhanced the anticancer effects of 5-FU in CT26 colon carcinoma, with a MOA involving apoptosis activation, senescence induction, and angiogenesis inhibition.[39]

Zuo Jin Wan (ZJW) is a TCM formula consisting of *Rhizoma Coptidis* and *Fructus Evodiae* in the ratio of 6:1 (w/w). The combination of chemotherapy with ZJW could reverse the drug resistance of HCT116/L-OHP cells, increase the sensitivity of HCT116/L-OHP cells to L-OHP, DDP, 5-FU, and MMC *in vitro*, and inhibit tumor growth in the colorectal cancer xenograft model, primarily through decreasing the P-gp level.[39]

Fuzheng-Yiliu granule (FYG) is a decoction that enhances the immune function and suppresses tumor growth. FYG consists of *Radix Hedydsari, Angelica sinensis* (Oliv.) Diels, *Curcuma zedoaria* (Christm.) Rosc., and *Patrinia heterophylla* Bunge. Interestingly, FYG plays a synergetic role with 5-FU in a colon cancer model, mainly through its effects on immune system regulation and energy metabolism, including increasing the number of white blood cells and lymphocytes, as well as cytokines in serum.[40]

Wenxia Changfu Formula (WCF) is composed of *Radix Aconiti Preparata, Radix et Rhizoma Rhei, Panax ginseng*, and *Angelica sinensis*. In a study conducted by Wang’s group, they used WCF-containing serum to treat nonsmall lung cancer cells with cisplatin and investigated the synergetic effects. The combination inhibited the overproliferation of A549 cell lines.
In the G0/G1 phase of the cell cycle by affecting the protein and mRNA expression of cyclin D1, PCNA, and Rb. In addition, it effectively inhibited the atrophy of the immune organs caused by chemotherapy, suggesting that WCF regulates other important signals in animals.\[41\]

In a clinical study, Dr. Xu et al. administered two different TCM decoctions with two chemotherapy drugs in Stage III and IV nonsmall cell lung cancer patients. Briefly, the patients were given a Kangliuzengxiao decoction (150 ml) twice a day during chemotherapy and continued with an oral intake of a Fuyanning decoction after chemotherapy. Meanwhile, a combination of Navelbine and cisplatin was used at the beginning of chemotherapy. The promising results showed that the patients benefited from the TCM decoction in several aspects, including median survival time, Karnofsky score, and the bone marrow hematopoietic system.\[42\]

**DISCUSSION AND PERSPECTIVES**

The TCM and drug interactions have drawn a great attention in many preclinical studies against various diseases including cancer, infectious diseases, and inflammatory diseases. Several reviews carefully analyzed the herb – drug interactions, the mechanisms, and the influence on pharmacokinetics.\[43,59\]

In this review, we collected the literatures related to the herb – drug interactions on cancer research and focused on the mechanism of the interactions. As shown in Table 1, there were many studies focusing on the pathways such as cell cycle arrest and cell death during cancer therapy. Importantly, these preclinical studies provided strong scientific evidence to apply these natural compounds to clinical trials. Indeed, several single compounds or TCM decoction have been approved to start clinical trials in the past few years. For instance, Theracurmin\[a\] (a bioavailable curcumin) and curcumin entered Phase I trial against gemcitabine-resistant pancreatic and biliary tract cancers, respectively.\[34,60\] Recently, the TCM formulation PHY906 combined with capecitabine also started Phase II trial as a second-line therapy against advanced pancreatic cancer.\[61\] The combination of capecitabine and PHY906 was also used in clinical trials of other cancers including unresectable hepatocellular carcinoma and gastrointestinal malignancies.\[62,63\]

Furthermore, the cancer cells contain many biological capabilities during tumorigenesis and chemotherapy. Other than cell death and cell cycle arrest, metastasis, angiogenesis, drug resistance, and inflammation are important hallmarks of cancers.\[64\] Since the TCM and natural compounds always target multiple signaling pathways, it will be necessary to consider the combination mechanisms other than single drug treatment. The development of PHY906 as complementary anticancer drug was a successful example. In addition, the application of modern technology such as nanotechnology to increase the bioactivity, the adsorption, and the delivery of TCM is another promising research field. In a recent study, (-)-epigallocatechin-3-O-gallate, a major ingredient of green tea, could form the stable micellar nanocomplexes with an anticancer antibody Herceptin\[\textsuperscript{b}\]. The combination resulted in better selectivity and longer half-life.\[65\] Furthermore, other biological molecules such as microRNAs, long noncoding RNAs, and circular RNA are important targets on therapeutic signaling pathways, which are still lacking research on TCMs.\[66,67\] Finally, researchers also should be encouraged to pay close attention to functional roles of TCM on cancer prevention, cancer stem cells, recurrence, etc.\[68\]

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**Conflicts of interest**

There are no conflicts of interest.

**References**


