Interactions Between Traditional Chinese Medicine and Anticancer Drugs in Chemotherapy

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Abstract

Herbal medicines, including traditional Chinese medicines (TCMs), have been used in Eastern countries for treating diseases such as cancer for thousands of years. With the growing knowledge of tumorigenesis and cancer therapy, some natural compounds have been developed as clinical anticancer drugs. In addition, many compounds and TCMs have been characterized as complementary and alternative treatments, with synergistic effects on enhancing the efficacy or reducing the side effects of the therapeutics. In this review, we summarized the recent studies focusing on the combination of natural compounds or TCM decoction with chemotherapy. The detailed mechanisms of action of the combinations and the application of analytical methods on TCM development are also discussed.

Keywords: Anticancer, interactions, natural compounds, traditional Chinese medicine, traditional Chinese medicine formulae

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.¹ 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 reigation, 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,² the effects of TCM as adjuvant treatment during chemo- or radio-therapy,³ the application of proteomics to study the mechanisms of TCM,⁴ and the molecular and cellular mechanisms of TCM in cell death pathways.⁵ 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.

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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 acylophloroglucinols (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 p21Waf1/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.[16] 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.[17]

Matrine is a compound obtained from Leguminosae, such as *Sophora flavescent* Ait, with anticancer activity arising from apoptotic induction and cell cycle arrest. As$_2$O$_3$, discovered from TCM, has been used for treating acute promyelocytic leukemia. When combined together, As$_2$O$_3$ exhibited synergetic effects with matrine on RPM18226 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.[22] 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 synergetic 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.[24] 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 elfF2α-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

| Chemicals          | Clinical drugs                  | Cancer types                          | Mechanism of action                                                      | References          |
|--------------------|---------------------------------|---------------------------------------|--------------------------------------------------------------------------|---------------------|
| **Single compounds** |                                 |                                       |                                                                          |                     |
| Curcumin           | Mitomycin C; docetaxel           | Breast cancer; lung cancer             | Induces cell cycle arrest by inhibiting cyclin D1, cyclin E, cyclin A, CDK2, and CDK4; reduces toxicity to bone marrow and liver in vivo | [6,7]               |
| Baicalein          | Doxorubicin                      | Breast cancer                         | Combined with nanostructure lipid carriers to increase cytotoxicity       | [8]                 |
| Celastrol          | TRAIL/APO-2L; ABT-737; SAHA; HSP90 inhibitor | Ovarian carcinoma; colorectal carcinoma; hepatocellular carcinoma; lung cancer; and glioblastoma | Induces apoptosis upregulation of DR4 and DR5, induces apoptosis through activating ER stress and NOXA, induces apoptosis through NF-κB inhibition and E-cadherin upregulation, and induces proteotoxic stress | [9-12]              |
| Gambogic acid      | Doxorubicin; 5-FU                 | Breast cancer; lung cancer; and ovarian cancer | Sensitizes drug-resistant cells through inhibiting P-gp and survivin; triggers both apoptosis and necroptosis via ROS and mitochondrial pathways | [13-15]             |
| Genistein          | Gemcitabine; erlotinib; 5-FU     | Pancreatic cancer                     | Inhibits NF-κB and Akt activation; induces apoptosis and autophagy        | [16-18]             |
| Guttiferone K      | 5-FU                             | Colon cancer                          | Induces G0/G1 cell cycle arrest and apoptosis by activating p21Waf1/Cip1   | [19]                |
| NCTD               | ABT-263; ABT-737                 | Neuroblastoma; hepatocellular carcinoma | Activates apoptosis through upregulation of NOXA; represses Mcl-1 mRNA level | [20,21]             |
| Matrine            | Arsenic trioxide                 | Myeloma cells                         | Activates apoptosis through activation of caspase-3 and PARP, upregulation of Bim, downregulation of Bcl-2 and phosphor-Akt | [22]                |
| Berberine          | 2-deoxy-D-glucose                | Breast cancer; colon cancer           | ATP energy depletion and disruption of UPR                               | [23]                |
| Triptolide         | Vasostatin 120-180; oxaliplatin; Cisplatin; TRAIL | Lung cancer; colon cancer; gastric cancer; pancreatic cancer | Activates apoptosis through upregulation of caspases, Bax, Bak, and Bad suppression of NF-κB; activates apoptosis through inhibiting nuclear translocation of β-catenin; activates apoptosis through mitochondrial pathways; activates apoptosis | [24-27]             |
| Cinnamaldehyde     | Oxaliplatin, 5-FU                | Colorectal carcinoma                  | Activates apoptosis through regulating drug-metabolizing genes           | [28]                |
| Bufalin            | 5-FU; topotecan; camptothecin; etoposide; vorinostat | Hepatocellular carcinoma; multiple myeloma cells | Activates apoptosis and reduces drug resistance; inhibits PARP1 activity | [29,30]             |
| Honokiol           | Ionizing radiation               | Colon cancer; cancer stem cells       | Inhibits notch signaling pathway and DCLK1                               | [31]                |
| β-elemene          | Cisplatin; etoposide             | Lung cancer                           | Activates apoptosis through Bcl-2 family proteins; activates apoptosis through p53 and p21 | [32,33]             |
| Crocin             | Cisplatin                        | Osteosarcoma                          | Inhibits invasion and activates apoptosis                                  | [34]                |
| **Traditional Chinese medicine extracts and formula** |                                 |                                       |                                                                          |                     |
| PHY906             | CPT-11                           | Colon cancer                          | Inhibits inflammation and promotes progenitor cell repopulation           | [35]                |
| Yang Zheng XiaoJi  | Cyclopamine                      | Nonsmall cell lung cancer             | Sonic hedgehog, EMT                                                      | [36]                |
| FWGE               | Cisplatin; docetaxel, 5-FU       | Ovarian carcinoma cells; hepatocellular carcinoma | Increases apoptosis and cytotoxicity through caspase-3 and caspase-7      | [37,38]             |
| TLBZT              | 5-FU                             | Colon carcinoma                       | Activates apoptosis, induces senescence, inhibits angiogenesis            | [39]                |
| ZJW                | L-OHP; DDP; 5-FU; mitomycin      | Colorectal cancer                     | Reverses drug resistance by decreasing P-gp level                         | [40]                |
| Fuzheng-Yiliu granules | 5-FU                          | Hepatoma                              | Induces apoptosis and increases white blood cell and lymphocyte            | [41]                |

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. 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. 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. In a recent report, genistein was shown to induce cell death through apoptosis and autophagy when combined with 5-FU. 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. 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. 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.

### Compounds 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. A similar synergetic effect and mechanism were also observed in ovarian cancer cells.

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.

Two studies reported that curcumin had a strong synergetic effect with gemcitabine in pancreatic adenocarcinoma. 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.

Bufalin, bufotalin, telocinobufagin, and cinobufagin are the main bufadienolides extracted from *Venenum Bufonis*. Among these compounds, bufalin exhibits anticancer activities against several types of cancer cells. Several studies suggested that bufalin could enhance the anticancer 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. In addition, Wu’s study indicated that bufalin was an effective PARP1 inhibitor and was able to enhance the efficacy of

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**Table 1: Contd...**

| Chemicals | Clinical drugs | Cancer types | Mechanism of action | References |
|-----------|----------------|--------------|---------------------|------------|
| CF        | Cisplatin      | Nonsmall cell lung cancer | G0/G1 cell cycle arrest by inhibiting cyclin D1, PCNA, and Rb | [42] |
| Kangliuzengxiao decoction; Feiyanning decoction | Navelbine; cisplatin | Lung cancer | Clinical study | [43] |

NCTD: Norcantharidin, FWGE: Fermented wheat germ extract, TLBZT: Teng-Long-Bu-Zhong-Tang, ZJW: Zuo Jin, Wan, WCF: Wenxia Changfu Formula, 5-FU: 5-fluorouracil, SAHA: Suberoylanilide hydroxamic acid, CPT: Camptothecin, NF-κB: Nuclear factor-κB, ROS: Reactive oxygen species, UPR: Unfolded protein response, DCLK1: Doublecortin-like kinase 1, EMT: Epithelial–mesenchymal transition, ER: Endoplasmic reticulum, P-gp: P-glycoprotein

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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 synergistic 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.\[39\] 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, Poria 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 MDR 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 Hedyosari, Angelica sinensis (Oliv.) Diels, Curcuma zedoaria (Christm.) Rosc., and Patrinia heterophylla Bunge. Interestingly, FYG plays a synergistic 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 Rhiza 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 synergistic 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 Kangluzenzxiao decoction (150 ml) twice a day during chemotherapy and continued with an oral intake of a Feyanning 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.\[43,49\] 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 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.\[41\] The combination of capecitabine and PHY906 was also used in clinical trials in other cancers including unresectable hepatocellular carcinoma and gastrointestinal malignancies.\[82,63\]

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\®. 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.\[84,67\] 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**

1. Newman DJ, Cragg GM. Natural products as sources of new drugs over the 30 years from 1981 to 2010. J Nat Prod 2012;75:311-35.
2. Wang CY, Bai XY, Wang CH. Traditional Chinese medicine: A treasured natural resource of anticancer drug research and development. Am J Chin Med 2014;42:543-59.
3. Qi F, Li A, Inagaki Y, Gao J, Li J, Kokudo N, et al. Chinese herbal medicines as adjuvant treatment during chemo- or radio-therapy for cancer. Biosci Trends 2010;4:297-307.
4. Lao Y, Wang X, Xu N, Zhang H, Xu H. Application of proteomics to determine the mechanism of action of traditional Chinese medicine remedies. J Ethnopharmacol 2014;155:1-8.
5. Wang X, Feng Y, Wang N, Cheung F, Tan HY, Zhong S, et al. Chinese medicines induce cell death: The molecular and cellular mechanisms for cancer therapy. Biomed Res Int 2014;2014:530342.
6. El-Rayes BF, Philip PA, Sarkar FH, Shields AF, Ferris AM, Hess K, et al. A phase II study of isoflavones, erlotinib, and gemcitabine in advanced pancreatic cancer. Invest New Drugs 2011;29:694-9.
7. Yu C, Liu SL, Qi MH, Zou X. Cinnamaldehyde/chemotherapeutic agents interaction and drug-metabolizing genes in colorectal cancer. Mol Med Rep 2014;9:669-76.
8. Kannamakkara AB, Guha S, Krishnan S, Diagaradjan P, Gelovani J, Aggarwal BB, et al. Curcumin potentiates antitumor activity of gemcitabine in an orthotopic model of pancreatic cancer through suppression of proliferation, angiogenesis, and inhibition of nuclear factor-kappaB-regulated gene products. Cancer Res 2007;67:3853-61.
9. Mahmoud AM, Yang W, Bosland MC. Soy isoflavones and prostate cancer: A review of molecular mechanisms. J Steroid Biochem Mol Biol 2014;140:116-32.
10. Banerjee S, Zhang Y, Ali S, Bhuiyan M, Wang Z, Chiao PJ, et al. Molecular evidence for increased antitumor activity of gemcitabine by genistein in vitro and in vivo using an orthotopic model of pancreatic cancer. Cancer Res 2005;65:9064-72.
11. El-Rayes BF, Ali S, Ali IF, Philip PA, Abbruzzese J, Sarkar FH, et al. Potentiation of the effect of erlotinib by genistein in pancreatic cancer: The role of Akt and nuclear factor-kappaB. Cancer Res 2006;66:10553-9.
12. Suzuki R, Kang Y, Li X, Roife D, Zhang R, Fleming JB, et al. Genistein potentiates the antitumor effect of 5-fluorouracil by inducing apoptosis and autophagy in human pancreatic cancer cells. Anticancer Res 2013;34:4685-92.
13. Su J, Cheng H, Zhang D, Wang M, Xie C, Hu Y, et al. Synergistic effects of 5-fluorouracil and gambogenic acid on A549 cells: Activation of cell death caused by apoptotic and necroptotic mechanisms via the ROS-mitochondria pathway. Biol Pharm Bull 2014;37:1259-68.
The natural κFermented wheat germ extract induced cell death and apoptosis. J Cancer 2013;13:707-16.

16. Wang J, Yuan Z. Gambogenic acid sensitizes ovarian cancer cells to doxorubicin through ROS-mediated apoptosis. Cell Biochem Biophys 2013;67:199-206.

17. Wang X, Gu Z, Li G, Zhang S, Cao Z, Yang Z, et al. Norcantharidin enhances ABT-263-mediated anticancer activity in neuroblastoma cells by upregulation of Noxa. Oncol Rep 2014;32:716-22.

18. Zhang S, Li G, Ma X, Wang Y, Liu G, Feng L, et al. Norcantharidin enhances ABT-737-induced apoptosis in hepatocellular carcinoma cells by transcriptional repression of Mel-1. Cell Signal 2012;24:1803-9.

19. Li X, Lao Y, Zhang H, Wang X, Tan H, Lin Z, et al. The natural compound gatifurterone S sensitizes prostate cancer to starvation induced apoptosis via calcium and JNK elevation. BMC Cancer 2015;15:254.

20. Lin Y, Yang X, Lu M, Zheng W, Zhang J, Zhaung H, et al. Herbal compound triptolide synergistically enhanced antitumor activity of vasosatinitin120-180. Anticancer Drugs 2013;24:945-58.

21. Li CJ, Chu CY, Huang LH, Wang MH, Sheu LF, Yeh JL, et al. Synergistic anticancer activity of triptolide combined with cisplatin exerts synergistic anti¬cancer activity in gastric cancer in vitro and in vivo. Cancer Lett 2013;319:203-13.

22. Liu Y, Xiao E, Yuan L, Li G. Triptolide synergistically enhances antitumor activity of oxaliplatin in colon carcinoma in vitro and in vivo. DNA Cell Biol 2014;33:418-25.

23. Borja-Cacho D, Yokoyama Y, Chugh RK, Mujumdar NR, Dudeja V, Clawson KA, et al. TRAIL and triptolide: An effective combination that induces apoptosis in pancreatic cancer cells. J Gastrointest Surg 2010;14:252-60.

24. Zhu H, Ding WJ, Wu R, Weng QJ, Lou JS, Jin RJ, et al. Synergistic anti-cancer activity by the combination of TRAIL/APO-2L and celestrol. Cancer Invest 2010;28:23-32.

25. Zhu H, Liu XW, Ding WJ, Xu DQ, Zhao YC, Wu L, et al. Up-regulation of death receptor 4 and 5 by celestrol enhances the anti-cancer activity of TRAIL/APO-2L. Cancer Lett 2010;297:155-64.

26. Zhu H, Yang W, He LJ, Ding WJ, Zheng L, Liao SD, et al. Upregulating noxa by ER stress, celestrol exerts synergistic anti-cancer activity in combination with ABT-737 in human hepatocellular carcinoma cells. PLoS One 2012;7:e52333.

27. Zheng L, Fu Y, Zhaung L, Gai R, Ma J, Lou J, et al. Simultaneous NF-xB inhibition and c-eadherin upregulation mediates mutually synergistic anticancer activity of celestrol and SAHA in vitro and in vivo. Int J Cancer 2014;135:1721-32.

28. Fan LX, Liu CM, Gao AH, Zhou YB, Li J. Berberine combined with 2-deoxy-d-glucose synergistically enhances cancer cell proliferation inhibition via energy depletion and unfolded protein response disruption. Biochim Biophys Acta 2013;1830:5175-83.

29. Gu W, Liu L, Fang FF, Huang F, Cheng BB, Li B, et al. Reversal effect of bufalin on multidrug resistance in human hepatocellular carcinoma BEL-7402/S-FU cells. Oncol Rep 2014;31:216-22.

30. Huang H, Cao Y, Wei W, Liu W, Lu SY, Chen YB, et al. Targeting poly-(ADP-ribose) polymerase partially contributes to bufalin-induced cell death in multiple myeloma cells. PLoS One 2013;8:e66130.

31. Yin H, Guo R, Xu Y, Zheng Y, Hou Z, Dai X, et al. Synergistic anticancer efficiency of docetaxel and curcumin against lung cancer. Acta Biochim Bioophys Sin (Shanghai) 2012;44:147-53.

32. Liu Q, Li J, Pu G, Zhang F, Liu H, Zhang Y, et al. Co-delivery of baicalein and doxorubicin by hyaluronic acid decorated nanoliposomes as a drug delivery vehicle for breast cancer therapy. Drug Deliv 2016;23:1364-6.

33. Li X, Huang T, Jiang G, Gong W, Qian H, Zou C, et al. Synergistic apoptotic effect of crocin and cisplatin on osteosarcoma cells via caspase induced apoptosis. Toxicol Lett 2013;221:197-204.

34. Kanai M, Yoshimura K, Aoda M, Inaiizumi A, Suzuki C, Matsumoto S, et al. A phase I/II study of gemicmatine-based chemotherapy plus curcin for patients with gemicmatine-resistant pancreatic cancer. Cancer Chemother Pharmacol 2011;68:157-64.

35. Lam W, Bussom S, Guan F, Jiang Z, Zhang W, Gullen EA, et al. The four-herb Chinese medicine PHY906 reduces chemotherapy-induced gastrointestinal toxicity. Sci Transl Med 2010;2:45ra59.

36. Wang CW, Wang CK, Chang YJ, Choong CY, Lin CS, Tai CJ, et al. Preclinical evaluation on the tumor suppression efficiency and combination drug effects of fermented wheat germ extract in human ovarian carcinoma cells. Evid Based Complement Alternat Med 2012;2012:570785.

37. Tai CJ, Wang WC, Wang CK, Wu CH, Yang MD, Chang YJ, et al. Fermented wheat germ extract induced cell death and enhanced cytotoxicity of cisplatin and 5-fluorouracil on human hepatocellular carcinoma cells. Evid Based Complement Alternat Med 2013;2013:121725.

38. Deng S, Hu B, An HM, Du Q, Xu L, Shen KP, et al. Teng-Long-Bu-Zhong-Tang, a Chinese herbal formula, enhances anticancer effects of 5-Fluorouracil in CT26 colon carcinoma. BMC Complement Altern Med 2013;13:128.

39. Sui H, Liu X, Jin BH, Pan SF, Zhou LH, Yu NA, et al. Zao Jin WAN, a traditional Chinese herbal formula, reverses P-gp-mediated MDR in vitro and in vivo. Evid Based Complement Alternat Med 2013;2013:957078.

40. Cao Z, Liao L, Chen X, Lan L, Hu H, Liu Z, et al. Enhancement of antitumor activity of low-dose 5-fluorouracil by combination with Fuzheng-Yilu granules in hepatoma 22 tumor-bearing mice. Integr Cancer Ther 2013;12:174-81.

41. Li XM, Ouyang B, Liu H, Liu GW, Wu ZC, Yu HY, et al. In vitro and in vivo inhibitory effect of the combination of Wenxia Changfu formula [see text] with cisplatin in non-small cell lung cancer. Chin J Integr Med 2011;17:908-16.

42. Xu ZY, Jin CJ, Zhou CC, Wang ZQ, Zhou WD, Deng HB, et al. Treatment of advanced non-small-cell lung cancer with Chinese herbal medicine by stages combined with chemotherapy. J Cancer Res Clin Oncol 2011;137:1117-22.

43. Fong SY, Wong YC, Xie C, Zuo Z. Herb-drug interactions between scutellaria radix and mefenamic acid: Simultaneous investigation of pharmacokinetics, anti-Inflammatory effect and gastric damage in rats. J Ethnopharmacol 2015;170:106-16.

44. Lao Y, Wang G, Liu Z, Wang X, Ruan P, Xu W, et al. The natural compound oblongifolin C inhibits autophagic flux and enhances antitumor efficacy of nutrient deprivation. Autophagy 2014;10:736-49.

45. Yu Q, Chen B, Zhang X, Qian W, Ye B, Zhou Y, et al. Arsenic trioxide-enhanced, matrine-induced apoptosis in multiple myeloma cell lines. Planta Med 2013;79:775-81.

46. Li XJ, Jiang ZZ, Zhang LY. Triptolide: Progress on research in pharmacodynamics and toxicology. J Ethnopharmacol 2014;155:67-79.

47. Kannaiyan R, Shannmugam MK, Sethi G. Molecular targets of celastrol derived from thunder of god vine: Potential role in the treatment of inflammatory disorders and cancer. Cancer Lett 2011;303:9-20.

48. Boridy S, Le PU, Petrecca K, Maysinger D. Celastrol targets proteostasis and acts synergistically with a heat-shock protein 90 inhibitor to kill human glioblastoma cells. Cell Death Dis 2014;5:e1216.

49. Zhou QM, Wang XF, Liu XJ, Zhang H, Lu YY, Su SB, et al. Curcumin enhanced antiproliferative effect of mitomycin C in human breast cancer MCF-7 cells in vitro and in vivo. Acta Pharmocol Sin 2011;32:1402-10.

50. Ponnurangam S, Mammen JM, Ramalingam S, He Z, Zhang Y, Umar S, et al. Honokiol in combination with radiation targets notch signaling to inhibit colon cancer stem cells. Mol Cancer Ther 2012;11:963-72.

51. Yao CC, Tu YR, Jiang J, Ye SF, Du HX, Zhang Y, et al. β-elemene reverses the drug resistance of lung cancer A549/DDP cells via the mitochondrial apoptosis pathway. Oncol Rep 2014;31:2311-8.

52. Zhang F, Xu L, Qu X, Zhao M, Jin B, Kang J, et al. Synergistic antitumor effect of β-elemene and etoposide is mediated via induction of cell apoptosis and cell cycle arrest in non-small cell lung carcinoma cells. Mol Med Rep 2011;4:1189-93.

53. Wang S, Wang L, Chen M, Wang Y. Gambogenic acid sensitizes resistant breast cancer cells to doxorubicin through inhibiting P-glycoprotein and suppressing survivin expression. Chem Biol Interact 2015;225:76-84.

54. Lev-Ari S, Vexler A, Starr A, Ashkenazy-Voghera M, Greif J, Aderka D, et al. Curcumin augments gemicmatine cytotoxic effect on pancreatic adenocarcinoma cell lines. Cancer Invest 2007;25:411-8.

55. Yin PH, Liu X, Qiu YY, Cai JF, Qin JM, Zhu HR, et al. Anti-tumor activity and apoptosis-regulation mechanisms of bufalin in various
cancers: New hope for cancer patients. Asian Pac J Cancer Prev 2012;13:5339-43.
56. Liu SH, Cheng YC. Old formula, new rx: The journey of PHY906 as cancer adjuvant therapy. J Ethnopharmacol 2012;140:614-23.
57. Wang E, Bussom S, Chen J, Quinn C, Bedognetti D, Lam W, et al. Interaction of a traditional Chinese medicine (PHY906) and CPT-11 on the inflammatory process in the tumor microenvironment. BMC Med Genomics 2011;4:38.
58. Jiang WG, Ye L, Ruge F, Sun PH, Sanders AJ, Ji K, et al. Expression of sonic hedgehog (SHH) in human lung cancer and the impact of YangZheng XiaoJi on SHH-mediated biological function of lung cancer cells and tumor growth. Anticancer Res 2015;35:1321-31.
59. Cheng BH, Zhou X, Wang Y, Chan JY, Lin HQ, Or PM, et al. Herb-drug interaction between an anti-HIV Chinese herbal SH formula and atazanavir in vitro and in vivo. J Ethnopharmacol 2015;162:369-76.
60. Kanai M, Otsuka Y, Otsuka K, Sato M, Nishimura T, Mori Y, et al. A phase I study investigating the safety and pharmacokinetics of highly bioavailable curcumin (Theracurmin) in cancer patients. Cancer Chemother Pharmacol 2013;71:1521-30.
61. Saif MW, Li J, Lamb L, Kaley K, Elligers K, Jiang Z, et al. First-in-human phase II trial of the botanical formulation PHY906 with capecitabine as second-line therapy in patients with advanced pancreatic cancer. Cancer Chemother Pharmacol 2014;73:373-80.
62. Yen Y, So S, Rose M, Saif MW, Chu E, Liu SH, et al. Phase I/II study of PHY906/capecitabine in advanced hepatocellular carcinoma. Anticancer Res 2009;29:4083-92.
63. Saif MW, Lansigan F, Ruta S, Lamb L, Mezes M, Elligers K, et al. Phase I study of the botanical formulation PHY906 with capecitabine in advanced pancreatic and other gastrointestinal malignancies. Phytomedicine 2010;17:161-9.
64. Hanahan D, Weinberg RA. Hallmarks of cancer: The next generation. Cell 2011;144:646-74.
65. Chung JE, Tan S, Gao SJ, Yongvongsoontorn N, Kim SH, Lee JH, et al. Self-assembled micellar nanocomplexes comprising green tea catechin derivatives and protein drugs for cancer therapy. Nat Nanotechnol 2014;9:907-12.
66. Hammond SM. An overview of microRNAs. Adv Drug Deliv Rev 2015;87:3-14.
67. Yarmishyn AA, Kurochkin IV. Long noncoding RNAs: A potential novel class of cancer biomarkers. Front Genet 2015;6:145.
68. Wang X, Wang N, Cheung F, Lao L, Li C, Feng Y, et al. Chinese medicines for prevention and treatment of human hepatocellular carcinoma: Current progress on pharmacological actions and mechanisms. Chin J Integr Med 2015;13:142-64.