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Anticancer and Overcoming Multidrug Resistance Activities of Potential Phytochemicals

Chi-Ming Liu[1#], MengQiao Su[1,2#], LiJie An[1,2], ZiChen Shao[1,2], ZhiLing Wu[3], NingChang Han[3], YuHan Ma[3] and Chung-Yi Chen[4*]

[1]*School of Medicine, Yichun University, Yichun 336000, Jiangxi Province, China.*

[2]*College of Chemistry and Bioengineering, Yichun University, Yichun 336000, Jiangxi Province, China.*

[3]*School of Aesthetic Medicine, Yichun University, Yichun 336000, Jiangxi Province, China.*

[4]*School of Medical and Health Sciences, Fooyin University, Kaohsiung, Taiwan.*

[#]*These authors contributed equally to this work.*

[*]Correspondence:
Chung-Yi Chen, School of Medical and Health Sciences, Fooyin University, Tel: +886-7-781-1151 (ext. 6200), Fax +886-7-783-4548.

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ABSTRACT

Cancer is a serious healthy issue worldwide and cause death to human. Drug resistance is a key factor for the successful treatment of various types of cancers. Phytochemicals have many pharmacological activities with low side effects. Several phytochemicals have been tested in clinical trials as chemosensitizers or anticancer drugs with low side effects. The molecular mechanism of anticancer and reversing multidrug resistance of phytochemicals by modulating signaling transduction or target gene expression are discussed in this article. In this study, we will review the pharmacological activities of natural compounds from herb with anticancer activities and multidrug resistance modulators including berberine, capsaicin, curcumin, 6-gingerol and piperine.

Keywords
Multidrug resistance, Apoptosis, Phytochemical, Combination therapy, Cancer stem cells.

Introduction
Cancer is a malignant disease, and the incidence of cancer has increased considerably in the world [1,2]. Genetic defects, diet, microbial infection, lifestyle factors, environmental pollution and other factors lead to cancer [3]. The treatments include surgical resection, chemotherapy, radiotherapy, and immunotherapy. It is difficult to avoid adverse effects of chemotherapeutic drugs. In addition, high doses of chemotherapy drugs can cause serious side effects. Combination therapy with chemotherapeutic agents is commonly used in various types of cancer. Combination therapy can reduce side effects and drug resistance through different mechanisms of action [4,5].

Traditional Chinese Medicine (TCM) has thousands history in China. In recent years, TCM has been widely accepted in many countries as complementary and alternative therapy for many diseases including chemotherapy. TCM is an alternative way to increase the quality of life for cancer patients. TCM has a variety of pharmacological activities, as well as from plants separated from the active ingredients with anti-cancer activities [6]. Spicy food is popular in some countries such as Thailand, China, India, Indonesia, and Colombia. Some studies have shown that intake of spicy food might help to prevent cancers. However, high-level spicy food intake might be associated with incidence of cancer [7]. Capsaicin, 6-gingerol, piperine, and curcumin are spicy ingredient. These phytochemicals exhibit anticancer properties in

tumor proliferation, angiogenesis, and other aspects. Many studies suggest that the phytochemicals isolated from spices or herb can be used for treatment of cancer.

Multidrug resistance is an important issue in the cancer therapy. Drug resistance can result from many mechanisms including host factors, specific genetic or cellular response to drug exposure. There are several mechanisms involved in acquired drug resistance in cancer cells [8]. These mechanisms include inhibition of apoptosis, increase of efflux transporters, and reduce of drug intake, inactivation of detoxification enzyme, drug inactivation, drug target alteration, and DNA damage repair (Figure 1). MRP1 (multidrug resistance associated protein 1), MRP2, glutathione transferase, MDR1/ABCB1 (multidrug resistance associated protein 1), and BCRP (breast cancer resistance protein) play a significant role in the development of multidrug resistance associated with intrinsic and acquired factors in many cancers [9]. Therefore, it is extremely important to look for new drugs that can enhance anti-cancer activity and overcome drug resistance.

Cell death can result from apoptosis, autophagy, or necrosis. Apoptosis is also called program cell death and it can trigger by extrinsic (death receptor) or/and intrinsic (mitochondrial) pathways. The apoptosis is induced by many factors including ultraviolet (UV) - radiation, DNA-damage, loss of growth factors and chemotherapy agents. Apoptosis has a various character including cell shrinkage, chromosome condensation and DNA fragmentation. Initiation of intrinsic or extrinsic pathway result in caspase activation. Caspase is cysteine protease that play an important role in apoptosis. Caspase-2, caspase-8, caspase-9 and caspase-10 are initiator caspases. Caspase-3, caspase-6, and caspase-7 are executioner caspases. Bcl-2 family consists anti-apoptotic proteins and pro-apoptotic proteins. P53 is tumor suppressor genes and it regulate cell growth, cell cycle and apoptosis. Loss of p53 function results in tumor formation and abnormal cell proliferation. The function of P-gp is associated with apoptosis. P-gp gene may be induced by mutated p53 during in tumor progression. It is important for chemotherapy agents to induce apoptosis during the treatment. Cancer resistance may result from aberrant over expression of Bcl-2. Inhibition of extrinsic pathway may develop chemoresistance. Several signaling pathways can modulate apoptosis and alter the sensitive of chemotherapy agents in cancer treatment (Figure 1). JNK, p38-MAPK, PI3K/AKT and NF-κB signaling pathway may involve in apoptosis.

Cancer stem cells (CSCs) was first found in hematopoietic system, and then found in prostate, breast, brain and other tissues. It has the unique ability of self-renewal, proliferation and differentiation. In different types of malignant tumors, CSC has a significant effect on tumor progression, drug resistance, recurrence and metastasis. Therefore, selective eradication of CSC is a promising strategy for cancer intervention. CSCs account for only about 1 % or even lower proportion in cancer, but compared with general cancer cells, CSCs are more tolerant and resistant to radiotherapy, chemotherapy and other treatments [10]. Studies showed that the epithelial-mesenchymal transition (EMT) pathway can induce tumor cells to produce CSCs with stemness; therefore, if EMT activation could be inhibited through the TGF-β or Wnt signaling pathways, then CSC proliferation could be reduced [11].

Studies have indicated that the phytochemicals can increase the sensitivity of cancer cells and overcome the drug resistance. Here, we introduce current knowledge and molecular mechanism of multidrug resistance and review the effects of phytochemicals with anticancer and overcoming the multidrug resistance activities. These phytochemicals are divided into two groups. One is spicy ingredient including 6-gingerol, capsaicin, curcumin, and piperine. The others are potential natural compounds from herb including berberine (Figure 2).

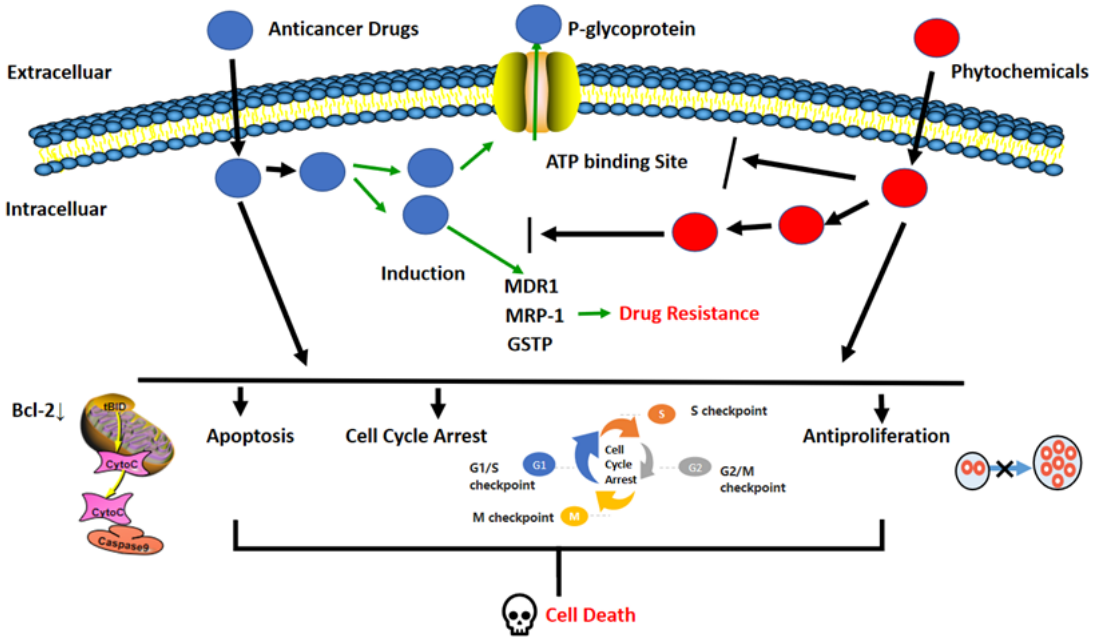

Figure 1: The mechanism of action of multidrug resistance in cancer cells.

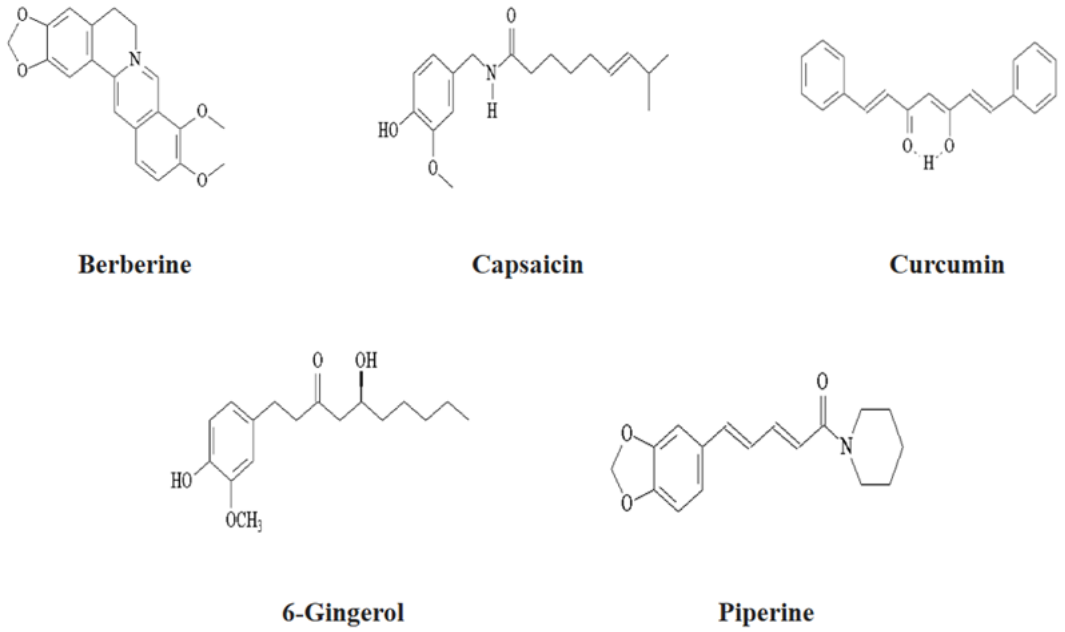

Figure 2: The chemical structure of berberine, capsaicin, curcumin, 6-gingerol and piperine.

Resistance mechanisms: ABC Transporters

P-glycoprotein (P-gp) is a 170 kDa transmembrane phosphorylated glycoprotein. P-glycoprotein transporter is also known as MDR1 (multidrug resistance associated protein 1) or ABCB1 (ATP-binding cassette subfamily B member 1). The role of P-gp is removed the endogenous and xenobiotic molecules from cells. P-gp is well expressed in organs including in liver, lungs, and the blood-brain barrier. The expression of P-gp can be induced by different stimulus factors such as drugs, free radicals, heat shock and UV exposure [12-14]. It was initially reported that tumor cells developed resistance to daunorubicin due to over-expression of P-gp by Dano et al. in 1973 [15]. Further, the surface glycoprotein of P-gp was identified and observed in several drug resistance cell lines by Juliano and Ling in 1976 [16]. P-gp is overexpression associated with resistance to anticancer drugs including colchicine, vinblastine, and doxorubicin in human KB carcinoma cells in 1987 [17]. It is widely believed that P-gp over expressed in drug-resistant tumor cells. Overexpression of P-gp can activate the ERK1/2, MAPK and PI3K signaling pathways and inhibit the apoptosis in drug-resistant cancer cells [18-20].

P-gp binds and interacts with many agents. Agents that are actively transported by P-gp are called substrates. Compounds that can reverse the drug resistance are called MDR modulators, MDR reversal agents, or MDR inhibitors. P-gp inhibitors act by blocking the substrate-binding site or altering the membrane composition[21]. The strategy to overcome anti-tumor drug resistance is to inhibit the efflux function of these transporters. Therefore, the identification and characterization of compounds with inhibitory effect of P-gp is a strategy for cancer therapy. Some drugs have P-gp inhibitory effects, including cyclosporine, quinoline, and calcium channel blockers [22,23]. There are three generations of P-gp inhibitors. The first generation of drugs are verapamil (VRP) and cyclosporin A. Verapamil was found to enhance and overcome the anticancer drug resistance in many cancer cell lines [24-26]. Owing to cardiovascular side effects, immunosuppressive side effects or ineffectiveness, the drugs have limitations in clinical application [27]. Dexverapamil, emopamil, gallopamil, and Ro11-2933 are the second generation of P-gp inhibitors [28,29]. These drugs have less cardiovascular side effects than the first generation. Based on the chemical structure activity, the third generation possesses more significant P-gp inhibition than the first and the second generations. However, these drugs need more clinical trials to examine these effects.

Glutathione transferase (GST) are multifunctional enzymes, which play an important role in biochemical processes. GSTs can conjugate glutathione (γ-L-glutamyl-L-cysteinyl-glycine, GSH). Glutathione transferase is also recognized as cellular detoxication enzymes against xenobiotics and noxious compounds. GSTs are in cytosol, mitochondrial and microsome. There are six cytosolic GSTs forms in human [30,31]. GSTs is highly expressed in chemotherapy-resistant cells such as bladder, ovarian, breast and colorectal cancer protecting tumor cells from apoptosis. In the previous studies, some anti-cancer drugs are the substrate for GST and these drugs are conjugated reaction with glutathione including cyclophosphamide, cisplatin, and busulfan et al [32]. In addition, GSTs is involved in signaling pathways such as cell survival and apoptosis. Some studies have shown that GSTs can modulate signaling pathways by interacting with mitogen-activated protein kinase (MAPK) [33,34]. The overexpression GSTs and activation of signal pathways might be associated with the resistance to apoptosis and chemoresistance in cancer cells. Therefore, the GST inhibitors should be designed, and GSTs inhibitors might be a potential and novel drug in chemotherapy.

MRP1, also called ABCC1, belongs to the ABCC (ABCC1 gene coding) subfamily. MRP1 was first identified in a small-cell lung

cancer cell line resistant to doxorubicin in 1992 [35]. Although MRP1 and P-gp have 23% similarity in their sequence, they have similarities in physiological and biochemical functions. In particular, MRP1 has been well expressed in a variety of tissues, and it can remove the xenobiotic molecules such as P-gp [36]. MRP1 is transcript by the MYCN oncogene. It has been reported that increased MRP1 levels in breast cancer and non-small cell lung cancer are associated with poor prognosis [37,38]. From a in vivo study, it indicated that MRP1 mediates chemoresistance [39].

Breast Cancer Resistance Protein was identified by Doyle in 1998 [40]. They found the resistant protein in MCF-7 cell line so named it as breast cancer resistance protein (BCRP). The function of BCRP is like that of P-gp and MRP1. BCRP can export xenobiotics and toxins from our body. BCRP is expressed in many organs including liver, testes, placenta, prostate, uterus, ovary, and small intestine. Elevated BCRP is associated with resistance of breast cancers to anticancer agents [41].

Potential Phytochemicals

Turmeric

Turmeric is widely cultured in Asia such as India and China. This plant can produce second metabolites including phenolic acids, flavonoids, and alkaloids with pharmacological activities. The well-known active compound from this plant is curcumin. Curcumin is a yellow pigment and polyphenolic compound, which is isolated from the rhizomes of *Curcuma zedoaria*, *Curcuma longa* and *Acorus calamus* L (Zingiberaceae), but has poor solubility [42]. Because curcumin is lipophilic and rapidly metabolized, the high dose of curcumin is applied to the use. Many researchers have improved curcumin delivery methods, including nanoparticle or liposome-encapsulated curcumin. Curcumin is traditionally used as a spice in food. Numerous studies have shown that curcumin has a variety of biological activities such as antioxidant and anticancer for the treatment of many types of cancer cells [43,44]. It is interesting that cancer cells are more sensitive with curcumin treatment than normal cells.

Curcumin induces apoptosis, inhibits angiogenesis, metastasis and antiproliferation in various cancer cells including prostate, breast and colorectal cancer cell [45]. A study reported that curcumin significantly decreased Bcl-2 expression and increased Bax expression through mitochondrial signaling pathway in breast cancer cell. Curcumin altered the ratio of Bax/Bcl-2 and resulted in cytochrome c release and induced caspase-3 and cleavage of poly (ADP-ribose) polymerase (PARP) activation in B-precursor lymphoblastic leukemia [46]. Moreover, curcumin decreased the expression of cIAP1 (cellular inhibitor of apoptosis protein-1) and XIAP (X-linked inhibitor of apoptosis protein). P53 interacts with Bcl-2 family proteins. Notch3 is overexpressed in many cancer cells including lung cancer and hepatocellular carcinoma. Curcumin induced apoptosis by activation of p53 and downregulation of Bcl-2 expression. Curcumin affected Notch3-p53 signaling pathway in mouse myeloma cells [47]. Curcumin caused apoptosis by activating p53 expression and decreasing MMP-2/9 expression in oral cancer [48]. Moreover, curcumin displayed synergistic effect in different cells through NF-κB-p53-caspase-3 or TLR4/MyD88 signaling pathway [49,50].

Curcumin can regulate onco-miRNA expression or tumor-suppressive miRNAs in different cancer cells. A study reported that curcumin decrease miR-21 expression and it further induced apoptosis by downregulating miR-21/PTEN/Akt signaling pathway in gastric cancer cells [51]. Additionally, curcumin increased RECK expression but decrease miR-21 expression through Wnt/β-catenin signaling pathway in osteosarcoma cell [52]. Curcumin also inhibited miR-21 expression by inducing PTEN in chronic myelogenous leukemia cells [53]. Overexpression of miR-125a-5p is associated with the development of nasopharyngeal carcinoma cells. Curcumin attenuated miR-125a-5p by inducing tumor protein p53 (TP53) expression in nasopharyngeal carcinoma cells [54]. MiR-27a is involved in cell migration, invasion, and proliferation in thymic carcinoma cells. Curcumin decreased miR-27a expression by blocking mTOR and Notch1 signaling pathways [55].

Curcumin can inhibit the growth, differentiation and self-renewal of cancer stem cells. It was found that curcumin down-regulated the expression of CD44, Nanog, Oct-4 (tumor markers), Bcl-2, Wnt pathway, the formation of tumor spheres and self-renewal ability of CSC, but up-regulated the expression of caspase-8, caspase-9, caspase-3, and Bax. Cancer stem cells (CSCs) and P-gp overexpression are associated with chemoresistance [56].

Curcumin has the inhibitory activities of P-gp, MRP1 and BCRP. S100 calcium-binding protein A8 (S100A8) is associated with MDR. Recently, a research indicated curcumin sensitized doxorubicin activity by inhibition of S100A8 and P-gp in chronic myeloid leukemia cells [57]. Curcumin treatment alone or combined with gemcitabine reversed the drug resistance and induced apoptosis, increased the expression of MRP2 and cleaved PARP, but decreased the expression of deoxycytidine kinase (DCK), TK1 (cytoplasmic thymidine kinase) and TK2 in bladder cancer cell line [58]. Upregulated miR-214 is associated with cisplatin resistance in ovarian cancer cells. Curcumin reversed the cisplatin-resistance ovarian cancer cells by regulating miR-214 expression [59]. Curcumin combined with vitamin D3 reduced the expression of aldehyde dehydrogenase-1 (ALDH-1) and P-gp. This combination enhanced tumor response to paclitaxel in drug resistance breast cancer cells [60]. A study has shown that combined treatment of curcumin and docetaxel has synergistic effect and this combination can modulate p53, PI3K, p-AKT, NF-κB, and COX-2 expression in prostate cancer cells [61]. Curcumin synergistically enhanced the cisplatin activity by activation of TRPM2 channel and mitochondrial oxidative stress in laryngeal squamous cancer cells [62]. In addition, co-treatment with curcumin and cisplatin has synergistic anticancer activity and induces apoptosis through ROS (reactive oxygen species)-mediated activation of ERK1/2 in bladder cancer cells [63]. These studies imply that combination treatment can reduce cytotoxicity and overcome multidrug resistance in many cancer cells.

From the in vitro and in vivo studies, these results imply that curcumin might have good anticancer activities. Additionally, curcumin was conducted in several clinical trials. Curcumin can be single use or in combination with chemotherapy agents. Different studies have shown curcumin at high dose could be tolerated and at low dose of curcumin have effects in some cancer cells. One study reported that 1440 mg/day of curcumin was taken by oral for prostate cancer patients [64]. The concentration of PSA was decreased during 6-month treatment. The high dose of curcumin is safe and well tolerated. A clinical study demonstrated that curcumin (8 g daily) is given to 25 pancreatic cancer patients. In this clinical trial, the expression of NF-κB, and COX-2 were suppressed in peripheral blood mononuclear cells from patients after curcumin treatment [65].

Ginger

Ginger is known as *Zingiber officinale* Roscoe and it belongs to Zingiberaceae family. It is widely cultivated in Asia including China, India, and Africa. Ginger is a spice with special odor, and it is very popular in Indian food. It is also used as medicine in China, Middle Eastern and Indian. Ginger is used to treat headache, cold, fever, constipation, asthma, and respiratory diseases. Gingerol, shogaol and paradol are biologically active compounds isolated from ginger rhizomes. Gingerols are the phenolic compounds and 6-gingerol is the main component. The pharmacological activities of gingerol and shogaols include anticancer, antioxidant, and anti-inflammatory effects.

6-Gingerol induce apoptosis and cell cycle arrest by p53 activation and proteasomal inhibition in HPV positive cervical cancer cells [66]. Moreover, 6-gingerol potentiate the cisplatin anticancer activity and it further inhibited xenograft tumor cells in vivo. 6-Gingerol also has chemopreventive properties. 6-Gingerol (2.5 μM/animal) activated Bax, p53, cytochrome c, caspases and apoptotic protease-activating factor-1 (Apaf-1) against benzo[a] pyrene-induced mouse skin tumorigenesis [67]. It is interesting that 6-gingerol induced apoptosis in mutated p53 expressing pancreatic cancer cells. It seems that 6-gingerol can inhibit tumor growth through p53-dependent or p53-independent signaling pathway [68]. Rastogi et al. reported that 6-gingerol inhibited mitochondrial respiratory complex I (MRCI) and generated reactive oxygen species (ROS) production [69]. 6-Gingerol treatment has significant cytotoxicity in several colon cancer cell lines. It has been observed that 6-gingerol elevated intracellular ROS and upregulated p53, p21, and p27 levels leading to cell cycle arrest in colon cancer cells [70].

Previous studies have shown that 6-gingerol can reverse the drug resistance in cancer cells. 6-Gingerol increased intracellular accumulation of daunorubicin and inhibited the P-gp activity in multidrug-resistant KB-C2 cancer cells [71]. Liu et al. have shown that 6-gingerol not only inhibited cancer cells growth but also reduced MRP1 and GST π protein expression in docetaxel resistant prostate cancer cells [72].

CSCs can resist traditional chemotherapy and radiotherapy, and its common mechanisms include increasing ABC transporter expression and low reactive oxygen species, activating anti-apoptotic pathways and DNA repair system [73]. Radiotherapy and chemotherapy can kill tumor cells by increasing ROS levels, but CSCs can reduce intracellular ROS levels and protect the toxicity of their own chemotherapy drugs.

Several studies have indicated 6-gingerol combined with chemotherapy agents have synergistic effects. 6-Gingerol combined with γ-tocotrienol augmented the anticancer activities by interfering with cell cycle distribution, inducing apoptosis, and downregulating the Wnt signaling pathway in human colorectal cancer cell lines [74]. The combination also modulated the ATF6, DDIT3, GADD34, FOXM1, CDK1 and p21 gene expression. In addition, 6-gingerol enhanced the anticancer activity of cisplatin in gastric cancer cells. The co-treatment inhibited cell migration, invasion and caused cell cycle arrest mediated PI3K/AKT signaling pathway [75]. Also describe 6-Gingerol synergized cytotoxicity of doxorubicin in liver cancer cells. The combination significantly induced cell cycle arrest at the G_2/M-phase. Moreover, 6-gingerol has vascular protective effect against doxorubicin-induced damage in isolated aortic rings [76].

Chili Pepper

Capsaicin is pungent alkaloids isolated from *Capsicum frutescens*. Capsaicin is used extensively as spices in many countries. Capsaicin exhibits anti-cancer, radio sensitizing and chemoprevention activity [77,78]. Additionally, capsaicin reduces pain or inflammation by topical application although capsaicin is irritating to the skin. Vanilloids (TRPV) is transient receptor potential (TRP) ion channels. TRP regulates many physiological or pathological conditions such as ROS, temperature, pH, and osmotic stress. Several phytochemicals such as capsaicin and piperine regulate the TRP ion channels. TRPV1 receptor is called capsaicin receptor. The anti-cancer activity of capsaicin is mediated TRPV1 receptor dependent or TRPV1 receptor independent manner. TRPV1 activation can cause cancer cell death associated with the Ca^{2+} influx. A previous study indicated capsaicin made mutant p53 protein degradation in mutp53-carrying cell line [79]. Bao et al. reported that capsaicin induces apoptosis by increasing p53 activation and AMPK expression via TRPV1-independent (AMPK-p53) pathways and TRPV1-dependent pathway in human osteosarcoma [80]. Capsaicin treatment mediated cell cycle arrest at G_0/G_1 phase and induced by activating p21, Bax, cleaved PARP and decreasing MDM2 expression in human colon cancer cells [77]. In addition, capsaicin inhibited androgen dependent prostate cancer cell growth by increasing expression of miR-449a. Elevated expression of miR-449a can further degrade and inactive the androgen receptor [81]. Capsaicin induced apoptosis and inhibited proliferation via downregulating NF-κB pathway in androgen-independent prostate cancer cells. The effect is not associated with p53 activation or involving in TRPV1 [82].

Capsaicin can overcome the multidrug resistance in cancer cells. Capsaicin increased intracellular accumulation of daunorubicin and vinblastine by inhibiting the P-gp efflux activity in drug -resistant

human KB-C2 cancer cells [71]. In addition, capsaicin enhanced the sensitivity of vinblastine in KB-C2 cells. This indicates that capsaicin reverses multidrug resistance by inhibiting P-gp activity. Li et al. demonstrated that the combination of capsaicin with piperine not only inhibited the P-gp activity of doxorubicin-resistant cancer cells, but also enhanced the sensitization activity of chemotherapy [83]. Another study has shown that capsaicin induced apoptosis by p53 activation and upregulating miR-34a expression in drug-resistant non-small cell lung carcinoma cells [84]. Capsaicin can down-regulate prostate cancer cell markers, inhibit the proliferation of PC3 and DU145 cancer stem cells in a dose-dependent manner, regulate Wnt / β-catenin pathway, and inhibit the growth activity of prostate cancer stem cells [85].

Capsaicin combined with chemotherapy agents were also reported in several studies. A study demonstrated that capsaicin and cisplatin displayed synergistically cytotoxic effects on human osteosarcoma. The combination caused cell cycle arrest, induced apoptosis and inhibited migration through ROS/JNK and p-AKT/mTOR signaling pathways [85]. Another study indicated that the combination induced higher apoptotic cell death and cell cycle arrest via aurora-A-mediated signaling pathway in cisplatin-resistant stomach cancer cells [86]. Hong et al. have demonstrated that the combination of capsaicin with 5-FU was significantly induce cell deaths through PI3K/AKT/mTOR signaling pathway [87]. Capsaicin combined with erlotinib induced synergistic cytotoxicity by inhibiting ERCC1 (excision repair cross-complementary 1) and AKT expression in human lung cancer cells [88].

Pepper

Piperine (1-Piperoylpiperidine) is dietary alkaloid and extracted from several plants including *Piper nigrum* Linn (black pepper) and *Piper longum* Linn (long pepper). Piperine is an important phytochemical from spicy food. Several studies have demonstrated that piperine has chemoprevention or anticancer actives in many cancer cells. Piperine treatment induced apoptosis by release of mitochondrial cytochrome c, activation of caspase-3, caspase-9, and cleaved PARP via partially via JNK/p38 MAPK-mediated intrinsic apoptotic pathway in human ovarian cancer cells [89]. Piperine induced apoptosis and it decreased androgen receptor and prostate specific antigen (PSA) levels in prostate cancer cells. Further, piperine inhibited p-STAT-3 and NF-κB transcription factors [90]. Piperine can regulate p53 expression and inhibit cell cycle proteins (CDK2, Cyclin A) to result in apoptosis and cell cycle arrest in breast cancer cells [91]. Additionally, piperine inhibited angiogenesis via PI3K /Akt signaling pathway in TRPV1-indenpent manner. It further shown that piperine inhibited phosphorylation of Ser 473 and Thr 308 residues of Akt [92] . Hwang et al. has indicated that piperine suppresses invasion by inhibition of MMP-9, PKCα, ERK1/2, phosphorylation, NF-κB and AP-1 nuclear translocation in human fibrosarcoma HT-1080 cells [93]. Human epidermal growth factor receptor 2 (HER2) overexpression could promote migration and invasion by inducing MMP-2 and MMP-9 expression. A study reported that piperine treatment inhibited HER2 gene expression by downregulating MMP-9, AP-1 and NF-κB transcription factors [94].

Piperine can enhance the toxicity of anticancer drugs to drug-resistant cells and reverse MDR through various mechanisms. MRP2 and BCRP are the main ATP-dependent transporters, which can reduce the intracellular concentration of many chemotherapeutic drugs and lead to multidrug resistance. Moreover, piperine enhances bioavailability of silybin by decreasing BCRP and MRP2 expression in Caco-2 and transfected MDCKII cell lines [95]. Piperine potentiated and re-sensitized the anticancer activity of doxorubicin and cisplatin in drug resistant cancer cells [96]. At the concentration of 50 μM piperine could reverse the resistance to doxorubicin 32.16 and 14.14 folds.

CSCs can repair its own eternal cells with high tumorigenicity, self-renewal and quickly adapt to changes in the surrounding environment. It has been reported that the combination of piperine and curcumin can inhibit the activity of breast cancer stem cells [97].

Piperine combined with chemotherapy agents are conducted in vivo and in vitro studies. Co-treatment of docetaxel and piperine had synergic cytotoxicity effects by inhibition of CYP3A4 activity in castration-resistant prostate cancer [98]. The combination did not have serious adverse effects on the animal. The similar results were also shown in the co-treatment of paclitaxel and piperine. The combination of paclitaxel (200 nM) with piperine (50 μM) displayed higher tumor growth inhibition by downregulating p-Akt and Mcl-1 expression [99]. Additionally, paclitaxel treatment with piperine had synergistic anti-cancer effect by upregulating cytochrome c, Bax and caspase-3 expression [100].

Berberine

Berberine is an isoquinoline alkaloid isolated from the roots, rhizomes and bark of *Coptis chinensis*. It has antiviral, antibacterial, antioxidant, anti-inflammatory, hypoglycemic and anticancer activities. In recent years, studies have found that berberine has inhibitory effect on a variety of tumors, including breast cancer, pancreatic cancer, lung cancer, rectal cancer and other tumors, with little side effects, and can inhibit tumor cell growth in vitro and in vivo experiments.

Berberine has anticancer activities in many cancer cells by in vitro and in vivo studies. Berberine induces apoptosis by increasing Bax, caspase-8, caspase-9 and caspase-3 expression [101,102]. Berberine increased phosphorylation of p53, XAF1, and GADD45α expression, which induced mitochondrial apoptosis [103]. Yu et al. have shown that berberine inhibited irinotecan-induced NF-κB activation and enhances irinotecan chemosensitivity in colon cancer [102]. Berberine promoted apoptosis by inducing NAG-1 and ATF3 expression through p53 dependent pathway [104]. Berberine can regulate microRNA expression in cancer cells and it further inhibit proliferation, invasion, or metastasis. Berberine induced transcription of miR-101 and inhibited growth and metastasis via COX-2/ PGE2 signaling pathways in endometrial cancer cells [105]. The overexpression of miR-21 was inhibited by berberine in colon cancer cells [106]. Berberine further induced integrin β4 (ITGβ4), programmed cell death 4 (PDCD4) expression

and apoptosis. The co-treatment of berberine and anticancer drugs provide synergistic effects. MicroRNA can enhance the sensitivity of chemotherapy agents. Berberine enhances the anti-cancer activity of cisplatin by upregulation of miR-203 [107]. Additionally, berberine sensitizes cisplatin activity via miR-93/PTEN/Akt signaling pathway by inhibiting miR-93 expression [108].

CSCs can activate the signaling pathways in the process of early embryonic development. Studies have found that signaling pathways regulating cell stem characteristics include Hedgehog, JAK / STAT, Nanog, Notch, PI3K / AKT and Wnt / β-catenin pathways. The activation of these signaling pathways enables CSCs to exert greater proliferation and migration ability. Berberine can inhibit the proliferation, invasion and metastasis of cancer cells by inactivating multiple signaling pathways. It has been found that the abnormal activation of Hedgehog signaling pathway plays an important role in the maintenance and proliferation of various tumors and tumor stem cells. Berberine can inhibit the growth of lung cancer cells and promote apoptosis in a dose-dependent manner by regulating Hedgehog signaling pathway [109]. Hypoxia can lead to drug resistance. High-dose berberine induces p53 activation through AMPK-HIF-1α-P-gp inactivation and reduces adriamycin resistance [110]. Berberine has synergistic effects with cisplatin, camptothecin and methyl methane sulfonate by downregulating XRCC1 expressions in breast cancer cells. This mechanism explains why berberine recovered the resistance cancer cells [111].

Conclusion

New drug development is a long and time-consuming process. Natural compounds play an important role in reversing the drug resistance and anticancer activities through various pharmacological mechanisms. Further, these bioactive compounds also possess potential chemosensitizing activity especially combined with chemotherapeutic agents. Although the phytochemicals are considered as safe agents, we should use the low concentrations of phytochemicals for the studies. Until now, there are still limitations in these studies. These studies are used high concentrations of phytochemicals in vitro study. It is important to develop and identify new drugs without significant cytotoxicity and side effects to cancer treatment and overcome the drug resistance.

Authors' Contributions

All the authors contributed to data collection, data analysis, writing, critical revision, and approved the final manuscript.

References

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018; 68: 394-424.
2. Fidler MM, Bray F, SoerjomataramI. The global cancer burden and human development: A review. Scand J Public Health. 2018; 46: 27-36.
3. Turnbull C, Sud A, Houlston RS. Cancer genetics, precision prevention and a call to action. Nat Genet. 2018; 50: 1212-1218.
4. Cheng YY, Hsieh CH, Tsai TH. Concurrent administration of anticancer chemotherapy drug and herbal medicine on the perspective of pharmacokinetics. J Food Drug Anal. 2018; 26: S88-S95.
5. Alimbetov D, Askarova S, Umbayev B, et al. Pharmacological targeting of cell cycle, apoptotic and cell adhesion signaling pathways implicated in chemoresistance of cancer cells. Int J Mol Sci. 2018; 19: 1690.
6. Wang Z, Qi F, Cui Y, et al. An update on Chinese herbal medicines as adjuvant treatment of anticancer therapeutics. Biosci Trends. 2018; 12: 220-239.
7. Chen YH, Zou XN, Zheng TZ, et al. High spicy food intake and risk of cancer: a meta-analysis of case-control studies. Chin Med J (Engl). 2017; 130: 2241-2250.
8. Minko T, Rodriguez-Rodriguez L, Pozharov V. Nanotechnology approaches for personalized treatment of multidrug resistant cancers. Adv Drug Deliv Rev. 2013; 65: 1880-1895.
9. Kumar A, Jaitak V. Natural products as multidrug resistance modulators in cancer. Eur J Med Chem. 2019; 176: 268-291.
10. Yang LX, Xing SJ, Dong MQ, et al. Research progress on anti-tumor strategies based on targeting tumor stem cells. Shandong Medical Journal. 2019; 59: 91-94.
11. Wu CH, Hong BH, Ho CT, et al. Targeting cancer stem cells in breast cancer: the potential anticancer properties of 6-shogaol and pterostilbene. J Agric Food Chem. 2015; 63: 2432-2441.
12. Chin KV, Tanaka S, Darlington G, et al. Heat shock and arsenite increase expression of the multidrug resistance (MDR1) gene in human renal carcinoma cells. J Biol Chem. 1990; 265: 221-226.
13. Uchiumi T, Kohno K, Tanimura H, et al. Involvement of protein kinase in environmental stress-induced activation of human multidrug resistance 1 (MDR1) gene promoter. FEBS Lett. 1993; 326: 11-16.
14. Uchiumi T, Kohno K, Tanimura H, et al. Enhanced expression of the human multidrug resistance 1 gene in response to UV light irradiation. Cell Growth Differ. 1993; 4: 147-157.
15. Dano K. Active outward transport of daunomycin in resistant Ehrlich ascites tumor cells. Biochim Biophys Acta. 1973; 323: 466-483.
16. Juliano RL, Ling V. A surface glycoprotein modulating drug permeability in Chinese hamster ovary cell mutants. Biochim Biophys Acta. 1976; 455: 152-162.
17. Ueda K, Cardarelli C, Gottesman MM, et al. Expression of a full-length cDNA for the human "MDR1" gene confers resistance to colchicine, doxorubicin, and vinblastine. Proc Natl Acad Sci U S A. 1987; 84: 3004-3008.
18. Yan T, Hu G, Wang A, et al. Paris saponin VII induces cell cycle arrest and apoptosis by regulating Akt/MAPK pathway and inhibition of P-glycoprotein in K562/ADR cells. Phytother Res. 2018; 32: 898-907.

19. Cai J, Chen S, Zhang W, et al. Salvianolic acid A reverses paclitaxel resistance in human breast cancer MCF-7 cells via targeting the expression of transgelin 2 and attenuating PI3 K/ Akt pathway. Phytomedicine. 2014; 21: 1725-1732.
20. Zhang Y, Qu XJ, Liu YP, et al. Reversal effect of PI3-K inhibitor LY294002 on P-glycoprotein-mediated multidrug resistance of human leukemia cell line K562/DNR and gastric cancer cell line SGC7901/ADR. Ai Zheng. 2009; 28: 97-99.
21. Drori S, Eytan GD, Assaraf YG. Potentiation of anticancer-drug cytotoxicity by multidrug-resistance chemosensitizers involves alterations in membrane fluidity leading to increased membrane permeability. Eur J Biochem. 1995; 228: 1020-1029.
22. Yu CP, Huang CY, Lin SP, et al. Activation of P-glycoprotein and CYP3A by Coptidis Rhizoma in vivo: using cyclosporine as a probe substrate in rats. J Food Drug Anal. 2018; 26: S125-S132.
23. Mollazadeh S, Sahebkar A, Hadizadeh F, et al. Structural and functional aspects of P-glycoprotein and its inhibitors. Life Sci. 2018; 214: 118-123.
24. Li P, Zhong D, Gong PY. Synergistic effect of paclitaxel and verapamil to overcome multi-drug resistance in breast cancer cells. Biochem Biophys Res Commun. 2019; 516: 183-188.
25. Zheng W, Li M, Lin Y, et al. Encapsulation of verapamil and doxorubicin by MPEG-PLA to reverse drug resistance in ovarian cancer. Biomed Pharmacother. 2018; 108: 565-573.
26. Williams JB, Buchanan CM, Pitt WG. Codelivery of doxorubicin and verapamil for treating multidrug resistant cancer cells. Pharm Nanotechnol. 2018; 6: 116-123.
27. Nabekura T. Overcoming multidrug resistance in human cancer cells by natural compounds. Toxins (Basel). 2010; 2: 1207-1224.
28. Alaoui-Jamali MA, Schecter RL, Rustum YM, et al. In vivo reversal of doxorubicin resistance by a new tiapamil analog Ro11-2933. J Pharmacol Exp Ther. 1993; 264: 1299-1304.
29. Pirker R, Keilhauer G, Raschack M, et al. Reversal of multi-drug resistance in human KB cell lines by structural analogs of verapamil. Int J Cancer. 1990; 45: 916-919.
30. Higgins LG, Hayes JD. Mechanisms of induction of cytosolic and microsomal glutathione transferase (GST) genes by xenobiotics and pro-inflammatory agents. Drug Metab Rev. 2011; 43: 92-137.
31. Board PG, Menon D. Glutathione transferases, regulators of cellular metabolism and physiology. Biochim Biophys Acta. 2013; 1830: 3267-3288.
32. Colvin OM, Friedman HS, Gamcsik MP, et al. Role of glutathione in cellular resistance to alkylating agents. Adv Enzyme Regul. 1993; 33: 19-26.
33. Pajaud J, Ribault C, Ben Mosbah I, et al. Glutathione transferases P1/P2 regulate the timing of signaling pathway activations and cell cycle progression during mouse liver regeneration. Cell Death Dis. 2015; 6: e1598.
34. Townsend DM, Findlay VL, Tew KD. Glutathione S-transferases as regulators of kinase pathways and anticancer drug targets. Methods Enzymol. 2005; 401: 287-307.
35. Cole SP, Bhardwaj G, Gerlach JH, et al. Overexpression of a transporter gene in a multidrug-resistant human lung cancer cell line. Science. 1992; 258: 1650-1654.
36. Maher JM, Slitt AL, Cherrington NJ, et al. Tissue distribution and hepatic and renal ontogeny of the multidrug resistance-associated protein (Mrp) family in mice. Drug Metab Dispos. 2005; 33: 947-955.
37. Filipits M, Pohl G, Rudas M, et al. Clinical role of multidrug resistance protein 1 expression in chemotherapy resistance in early-stage breast cancer: the Austrian Breast and Colorectal Cancer Study Group. J Clin Oncol. 2005; 23: 1161-1168.
38. Li J, Li ZN, Du YJ, et al. Expression of MRP1, BCRP, LRP, and ERCC1 in advanced non-small-cell lung cancer: correlation with response to chemotherapy and survival. Clin Lung Cancer. 2009; 10: 414-421.
39. Burkhart CA, Watt F, Murray J, et al. Small-molecule multidrug resistance-associated protein 1 inhibitor reversan increases the therapeutic index of chemotherapy in mouse models of neuroblastoma. Cancer Res. 2009; 69: 6573-6580.
40. Doyle LA, Yang W, Abruzzo LV, et al. A multidrug resistance transporter from human MCF-7 breast cancer cells. Proc Natl Acad Sci U S A. 1998; 95: 15665-15670.
41. Vtorushin SV, Khristenko KY, Zavyalova MV, et al. The phenomenon of multi-drug resistance in the treatment of malignant tumors. Exp Oncol. 2014; 36: 144-156.
42. Kharat M, Du Z, Zhang G, et al. Physical and chemical stability of curcumin in aqueous solutions and emulsions: impact of pH, temperature, and molecular environment. J Agric Food Chem. 2017; 65: 1525-1532.
43. Liu Y, Wang X, Zeng S, et al. The natural polyphenol curcumin induces apoptosis by suppressing STAT3 signaling in esophageal squamous cell carcinoma. J Exp Clin Cancer Res. 2018; 37: 303.
44. Samarghandian S, Azimi-Nezhad M, Farkhondeh T, et al. Anti-oxidative effects of curcumin on immobilization-induced oxidative stress in rat brain, liver and kidney. Biomed Pharmacother. 2017; 87: 223-229.
45. Subramaniam S, Selvaduray KR, Radhakrishnan AK. Bioactive compounds: natural defense against cancer? Biomolecules. 2019; 9: 758.
46. Kuttikrishnan S, Siveen KS, Prabhu KS, et al. Curcumin induces apoptotic cell death via inhibition of PI3-Kinase/ AKT pathway in B-precursor acute lymphoblastic leukemia. Front Oncol. 2019; 9: 484.
47. Zhang Y, Lin XY, Zhang JH, et al. Apoptosis of mouse myeloma cells induced by curcumin via the Notch3-p53 signaling axis. Oncol Lett. 2019; 17: 127-134.
48. Lee AY, Fan CC, Chen YA, et al. Curcumin Inhibits Invasiveness and Epithelial-Mesenchymal Transition in Oral Squamous Cell Carcinoma Through Reducing Matrix Metalloproteinase 2, 9 and Modulating p53-E-Cadherin Pathway. Integr Cancer Ther. 2015; 14: 484-490.

49. Dang YP, Yuan XY, Tian R, et al. Curcumin improves the paclitaxel-induced apoptosis of HPV-positive human cervical cancer cells via the NF-kappaB-p53-caspase-3 pathway. Exp Ther Med. 2015; 9: 1470-1476.
50. Zhang L, Tao X, Fu Q, et al. Curcumin inhibits cell proliferation and migration in NSCLC through a synergistic effect on the TLR4/MyD88 and EGFR pathways. Oncol Rep. 2019; 42: 1843-1855.
51. Qiang Z, Meng L, Yi C, et al. Curcumin regulates the miR-21/PTEN/Akt pathway and acts in synergy with PD98059 to induce apoptosis of human gastric cancer MGC-803 cells. J Int Med Res. 2019; 47: 1288-1297.
52. Zhou L, Lu Y, Liu JS, et al. The role of miR-21/RECK in the inhibition of osteosarcoma by curcumin. Mol Cell Probes. 2020: 51: 101534.
53. Taverna S, Giallombardo M, Pucci M, et al. Curcumin inhibits in vitro and in vivo chronic myelogenous leukemia cells growth: a possible role for exosomal disposal of miR-21. Oncotarget. 2015; 6: 21918-21933.
54. Gao W, Chan JY, Wong TS. Curcumin exerts inhibitory effects on undifferentiated nasopharyngeal carcinoma by inhibiting the expression of miR-125a-5p. Clin Sci (Lond). 2014; 127: 571-579.
55. Han Z, Zhang J, Zhang K, et al. Curcumin inhibits cell viability, migration, and invasion of thymic carcinoma cells via downregulation of microRNA-27a. Phytother Res. 2020; 34: 1629-1637.
56. Yang LX WL, Wang J P, et al. Research progress in targeting cancer stem cells by phytochemicals. Chemistry & Bioengineering. 2021; 38: 1-7.
57. Yang L, Li D, Tang P, et al. Curcumin increases the sensitivity of K562/DOX cells to doxorubicin by targeting S100 calcium-binding protein A8 and P-glycoprotein. Oncol Lett. 2020; 19: 83-92.
58. Cho CJ, Yang CW, Wu CL, et al. The modulation study of multiple drug resistance in bladder cancer by curcumin and resveratrol. Oncol Lett. 2019; 18: 6869-6876.
59. Zhang J, Liu J, Xu X, et al. Curcumin suppresses cisplatin resistance development partly via modulating extracellular vesicle-mediated transfer of MEG3 and miR-214 in ovarian cancer. Cancer Chemother Pharmacol. 2017; 79: 479-487.
60. Attia YM, El-Kersh DM, Ammar RA, et al. Inhibition of aldehyde dehydrogenase-1 and p-glycoprotein-mediated multidrug resistance by curcumin and vitamin D3 increases sensitivity to paclitaxel in breast cancer. Chem Biol Interact. 2019; 315: 108865.
61. Banerjee S, Singh SK, Chowdhury I, et al. Combinatorial effect of curcumin with docetaxel modulates apoptotic and cell survival molecules in prostate cancer. Front Biosci (Elite Ed). 2017; 9: 235-245.
62. Gokce Kutuk S, Gokce G, Kutuk M, et al. Curcumin enhances cisplatin-induced human laryngeal squamous cancer cell death through activation of TRPM2 channel and mitochondrial oxidative stress. Sci Rep. 2019; 9: 17784.
63. Park BH, Lim JE, Jeon HG, et al. Curcumin potentiates antitumor activity of cisplatin in bladder cancer cell lines via ROS-mediated activation of ERK1/2. Oncotarget. 2016; 7: 63870-63886.
64. Choi YH, Han DH, Kim SW, et al. A randomized, double-blind, placebo-controlled trial to evaluate the role of curcumin in prostate cancer patients with intermittent androgen deprivation. Prostate. 2019; 79: 614-621.
65. Dhillon N, Aggarwal BB, Newman RA, et al. Phase II trial of curcumin in patients with advanced pancreatic cancer. Clin Cancer Res. 2008; 14: 4491-4499.
66. Rastogi N, Duggal S, Singh SK, et al. Proteasome inhibition mediates p53 reactivation and anti-cancer activity of 6-gingerol in cervical cancer cells. Oncotarget. 2015; 6: 43310-43325.
67. Nigam N, George J, Srivastava S, et al. Induction of apoptosis by [6]-gingerol associated with the modulation of p53 and involvement of mitochondrial signaling pathway in B[a] P-induced mouse skin tumorigenesis. Cancer Chemother Pharmacol. 2010; 65: 687-696.
68. Park YJ, Wen J, Bang S, et al. [6]-Gingerol induces cell cycle arrest and cell death of mutant p53-expressing pancreatic cancer cells. Yonsei Med J. 2006; 47: 688-697.
69. Rastogi N, Gara RK, Trivedi R, et al. (6)-Gingerolinduced myeloid leukemia cell death is initiated by reactive oxygen species and activation of miR-27b expression. Free Radic Biol Med. 2014; 68: 288-301.
70. Lin CB, Lin CC, Tsay GJ. 6-Gingerol inhibits growth of colon cancer cell lovo via Induction of G2/M arrest. Evid Based Complement Alternat Med. 2012; 2012: 326096.
71. Nabekura T, Kamiyama S, Kitagawa S. Effects of dietary chemopreventive phytochemicals on P-glycoprotein function. Biochem Biophys Res Commun. 2005; 327: 866-870.
72. Liu CM, Kao CL, Tseng YT, et al. Ginger phytochemicals inhibit cell growth and modulate drug resistance factors in docetaxel resistant prostate cancer cell. Molecules. 2017; 22. 1477.
73. Li C, Xu BH. Research progress in clinical application of tumor stem cells. Chin J of Oncol Prev and Treat. 2021; 13: 01-06.
74. Yusof KM, Makpol S, Fen LS, et al. Suppression of colorectal cancer cell growth by combined treatment of 6-gingerol and gamma-tocotrienol via alteration of multiple signalling pathways. J Nat Med. 2019; 73: 745-760.
75. Luo Y, Zha L, Luo L, et al. [6]-Gingerol enhances the cisplatin sensitivity of gastric cancer cells through inhibition of proliferation and invasion via PI3K/AKT signaling pathway. Phytother Res. 2019; 33: 1353-1362.
76. Al-Abbasi FA, Alghamdi EA, Baghdadi MA, et al. Gingerol synergizes the cytotoxic effects of doxorubicin against liver cancer cells and protects from its vascular toxicity. Molecules. 2016; 21: 886.
77. Aggarwal BB, Shishodia S. Molecular targets of dietary agents for prevention and therapy of cancer. Biochem Pharmacol. 2006; 71: 1397-1421.

78. Aggarwal BB, Van Kuiken ME, Iyer LH, et al. Molecular targets of nutraceuticals derived from dietary spices: potential role in suppression of inflammation and tumorigenesis. Exp Biol Med (Maywood). 2009; 234: 825-849.
79. Garufi A, Pistritto G, Cirone M, et al. Reactivation of mutant p53 by capsaicin, the major constituent of peppers. J Exp Clin Cancer Res. 2016; 35: 136.
80. Bao Z, Dai X, Wang P, et al. Capsaicin induces cytotoxicity in human osteosarcoma MG63 cells through TRPV1-dependent and -independent pathways. Cell Cycle. 2019; 18: 1379-1392.
81. Zheng L, Chen J, Ma Z, et al. Capsaicin causes inactivation and degradation of the androgen receptor by inducing the restoration of miR-449a in prostate cancer. Oncol Rep. 2015; 34: 1027-1034.
82. Mori A, Lehmann S, O'Kelly J, et al. Capsaicin, a component of red peppers, inhibits the growth of androgen-independent, p53 mutant prostate cancer cells. Cancer Res. 2006; 66: 3222-3229.
83. Li H, Krstin S, Wang S, et al. Capsaicin and piperine can overcome multidrug resistance in cancer cells to doxorubicin. Molecules. 2018; 23: 557.
84. Chakraborty S, Mazumdar M, Mukherjee S, et al. Restoration of p53/miR-34a regulatory axis decreases survival advantage and ensures Bax-dependent apoptosis of non-small cell lung carcinoma cells. FEBS Lett. 2014; 588: 549-559.
85. Wang Y, Deng X, Yu C, et al. Synergistic inhibitory effects of capsaicin combined with cisplatin on human osteosarcoma in culture and in xenografts. J Exp Clin Cancer Res. 2018; 37: 251.
86. Huh HC, Lee SY, Lee SK, et al. Capsaicin induces apoptosis of cisplatin-resistant stomach cancer cells by causing degradation of cisplatin-inducible Aurora-A protein. Nutr Cancer. 2011; 63: 1095-1103.
87. Hong ZF, Zhao WX, Yin ZY, et al. Capsaicin enhances the drug sensitivity of cholangiocarcinoma through the inhibition of chemotherapeutic-induced autophagy. PLoS One. 2015; 10: e0121538.
88. Chen JC, Ko JC, Yen TC, et al. Capsaicin enhances erlotinib-induced cytotoxicity via AKT inactivation and excision repair cross-complementary 1 (ERCC1) down-regulation in human lung cancer cells. Toxicol Res (Camb). 2019; 8: 459-470.
89. Si L, Yang R, Lin R, et al. Piperine functions as a tumor suppressor for human ovarian tumor growth via activation of JNK/p38 MAPK-mediated intrinsic apoptotic pathway. Biosci Rep. 2018; 38: BSR20180503.
90. Samykutty A, Shetty AV, Dakshinamoorthy G, et al. Piperine, a bioactive component of pepper spice exerts therapeutic effects on androgen dependent and androgen independent prostate cancer cells PLoS One. 2013; 8: e65889.
91. Grinevicius V, Andrade KS, Mota N, et al. CDK2 and Bcl-xL inhibitory mechanisms by docking simulations and anti-tumor activity from piperine enriched supercritical extract. Food Chem Toxicol. 2019; 132: 110644.
92. Doucette CD, Hilchie AL, Liwski R, et al. Piperine, a dietary phytochemical, inhibits angiogenesis. J Nutr Biochem. 2013; 24: 231-239.
93. Hwang YP, Yun HJ, Kim HG, et al. Suppression of phorbol-12-myristate-13-acetate-induced tumor cell invasion by piperine via the inhibition of PKCalpha/ERK1/2-dependent matrix metalloproteinase-9 expression. Toxicol Lett. 2011; 203: 9-19.
94. Do MT, Kim HG, Choi JH, et al. Antitumor efficacy of piperine in the treatment of human HER2-overexpressing breast cancer cells. Food Chem. 2013; 141: 2591-2599.
95. Bi X, Yuan Z, Qu B, et al. Piperine enhances the bioavailability of silybin via inhibition of efflux transporters BCRP and MRP2. Phytomedicine. 2019; 54: 98-108.
96. Li S, Lei Y, Jia Y, et al. Piperine, a piperidine alkaloid from Piper nigrum re-sensitizes P-gp, MRP1 and BCRP dependent multidrug resistant cancer cells. Phytomedicine. 2011; 19: 83-87.
97. Ren J M JHY, Tang J L, Li M T, et al. Research progress on curcumin in antitumor and reversing multidrug resistance. China Pharmacist. 2013; 16: 1582-1585.
98. Makhov P, Golovine K, Canter D, et al. Co-administration of piperine and docetaxel results in improved anti-tumor efficacy via inhibition of CYP3A4 activity. Prostate. 2012; 72: 661-667.
99. Xie Z, Wei Y, Xu J, et al. Alkaloids from Piper Nigrum synergistically enhanced the effect of paclitaxel against paclitaxel-resistant cervical cancer cells through the downregulation of Mcl-1. J Agric Food Chem. 2019; 67: 5159-5168.
100. Pal MK, Jaiswar SP, Srivastav AK, et al. Synergistic effect of piperine and paclitaxel on cell fate via cyt-c, Bax/Bcl-2-caspase-3 pathway in ovarian adenocarcinomas SKOV-3 cells. Eur J Pharmacol. 2016; 791: 751-762.
101. You X, Cao X, Lin Y. Berberine enhances the radiosensitivity of hepatoma cells by Nrf2 pathway. Front Biosci (Landmark Ed). 2019; 24: 1190-1202.
102. Yu M, Tong X, Qi B, et al. Berberine enhances chemosensitivity to irinotecan in colon cancer via inhibition of NFkappaB. Mol Med Rep. 2014; 9: 249-254.
103. Park GB, Park SH, Kim D, et al. Berberine induces mitochondrial apoptosis of EBV-transformed B cells through p53-mediated regulation of XAF1 and GADD45alpha. Int J Oncol. 2016; 49: 411-421.
104. Piyanuch R, Sukhthankar M, Wandee G, et al. Berberine, a natural isoquinoline alkaloid, induces NAG-1 and ATF3 expression in human colorectal cancer cells. Cancer Lett. 2007; 258: 230-240.
105. Wang Y, Zhang S. Berberine suppresses growth and metastasis of endometrial cancer cells via miR-101/COX-2. Biomed Pharmacother. 2018; 103: 1287-1293.
106. Lu Y, Han B, Yu H, et al. Berberine regulates the microRNA-21-ITGBeta4-PDCD4 axis and inhibits colon cancer

viability. Oncol Lett. 2018; 15: 5971-5976.

107. You HY, Xie XM, Zhang WJ, et al. Berberine modulates cisplatin sensitivity of human gastric cancer cells by upregulation of miR-203. In Vitro Cell Dev Biol Anim. 2016; 52: 857-863.

108. Chen Q, Qin R, Fang Y, et al. Berberine sensitizes human ovarian cancer cells to cisplatin through miR-93/PTEN/Akt signaling pathway. 2015; 36: 956-965.

109. Sun Y Z LZ, Yuan Z, et al. Effect of berberine on proliferation and apoptosis of lung cancer stem cells and its mechanism. Chinese Journal of Tissue Engineering Research 2017; 21: 1313-1318.

110. Pan Y, Shao D, Zhao Y, et al. Berberine Reverses Hypoxia-induced Chemoresistance in Breast Cancer through the Inhibition of AMPK- HIF-1alpha. Int J Biol Sci. 2017; 13: 794-803.

111. Gao X, Wang J, Li M, et al. Berberine attenuates XRCC1-mediated base excision repair and sensitizes breast cancer cells to the chemotherapeutic drugs. J Cell Mol Med. 2019; 23: 6797-6804.

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