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REVIEW ARTICLE

Natural compounds as potential adjuvants to cancer therapy: Preclinical evidence

Shian-Ren Lin[1] (iD) | Chia-Hsiang Chang[1] | Che-Fang Hsu[1,2] | May-Jwan Tsai[3] | Henrich Cheng[3] | Max K. Leong[4] | Ping-Jyun Sung[5] | Jian-Chyi Chen[6] | Ching-Feng Weng[5,7] (iD)

[1]Department of Life Science and Institute of Biotechnology, National Dong Hwa University, Hualien, Taiwan

[2]Center for Prevention and Therapy of Gynaecological Cancers, Department of Research, Tzu Chi Hospital, Hualien, Taiwan

[3]Neural Regeneration Laboratory, Neurological Institute, Taipei Veterans General Hospital, Taipei City, Taiwan

[4]Department of Chemistry, National Dong Hwa University, Hualien, Taiwan

[5]Graduate Institute of Marine Biotechnology, National Dong Hwa University, Pingtung, Taiwan

[6]Department of Biotechnology, Southern Taiwan University of Science and Technology, Tainan City, Taiwan

[7]Department of Basic Medical Science, Center for Transitional Medicine, Xiamen Medical College, Xiamen, China

Correspondence
Ching-Feng Weng, Department of Basic Medical Science, Center for Transitional Medicine, Xiamen Medical College, Xiamen 361023, China.
Email: cfweng-cfweng@hotmail.com

Traditional chemotherapy is being considered due to hindrances caused by systemic toxicity. Currently, the administration of multiple chemotherapeutic drugs with different biochemical/molecular targets, known as combination chemotherapy, has attained numerous benefits like efficacy enhancement and amelioration of adverse effects that has been broadly applied to various cancer types. Additionally, seeking natural-based alternatives with less toxicity has become more important. Experimental evidence suggests that herbal extracts such as *Solanum nigrum* and *Claviceps purpurea* and isolated herbal compounds (e.g., curcumin, resveratrol, and matairesinol) combined with antitumoral drugs have the potential to attenuate resistance against cancer therapy and to exert chemoprotective actions. Plant products are not free of risks: Herb adverse effects, including herb–drug interactions, should be carefully considered.

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1 | INTRODUCTION

In clinics, chemotherapy for cancer patients is commonly based on the drug indications, recommended dosages, treatment duration, and adverse effects (e.g., nephrotoxicity and hepatotoxicity; Grossi et al., 2010; Sharbaf, Farhangi, & Assadi, 2017; Sulthana et al., 2017). Occasionally, it is difficult to prevent occurrences of adverse effects from chemotherapeutic drugs during therapy. For instance, doxorubicin, a widely used chemotherapy agent, frequently induces cardiomyopathy and chronic heart failure with a prevalence between 4% and 36%

(cardiomyopathy) and 0.2–8.7% (chronic heart failure) according to cumulative doses (Chatterjee, Zhang, Honbo, & Karliner, 2010; Volkova & Russell, 2011; J. Yu et al., 2018). Although there are reports of nephrotoxicity and immunosuppression from cisplatin during treatment, it is, nevertheless, a first choice for the treatment of advanced non-small-cell lung cancer cells (NSCLC), breast cancer and ovarian cancer (Brown et al., 2013; Browning et al., 2017; Lorusso, Petrelli, Coinu, Raspagliesi, & Barni, 2014; Manohar & Leung, 2018). Moreover, cancer cells may develop drug resistance during treatment with chemotherapy. Accordingly, higher doses need to be applied to achieve a similar tumoricidal effect as the initial dosage. Frequently, higher dosages have a higher possibility of severe side effects (Zheng, 2017). Consequently, taking a combination of drugs with different mechanisms could synergistically potentiate therapeutic efficacy (Glasgow & Chougule, 2015).

Currently, combinations of chemotherapeutic drugs are widely used for various cancer types (Liu et al., 2017; Zhang et al., 2011). Importantly, the advantage of using multiple drugs are seen as the lowering of doses which could lead to lower resistance and the retention of the same efficacy or sometimes a higher efficacy, a synergistic effect (Glasgow & Chougule, 2015; He et al., 2015; Liboiron & Mayer,

2014). The effects of lower toxicity are ignored as they are considered to be harmless. In fact, the accumulation of toxicity from each drug can still cause deleterious systemic responses (F. Li & Zhang, 2015). Therefore, optimizing drug ratios and schedules can provide an opportunity to improve drug combination activity and reduce dosages to attenuate toxicity (L. Wu, Leng, Cun, Foged, & Yang, 2017). Additionally, drug combinations which include dietary supplements and natural products have been postulated to obtain similar effects to conventional chemotherapeutic drugs but with less adverse effects (Lin, Fu, Tsai, Cheng, & Weng, 2017). Three meta-analyses reviewing traditional herbal medicine have found such products used as chemotherapeutic adjuvants in nasopharyngeal, breast, and pancreatic cancer treatments. The effective outcome has exemplified traditional herbal medicine as a chemotherapeutic adjuvant (W. Kim, Lee, Lee, Min, Baek, et al., 2015a; W. Kim, Lee, Lee, Min, Lee, & Cho, 2015b; Kuo et al., 2018). Since 2006, several clinical trials were conducted to assess the enhancing effect of natural compounds such as curcumin or traditional Chinese medicine (TCM) in promoting conventional chemotherapy against various cancers, including lung cancer (especially non-small-cell lung cancer), breast cancer, and colon cancer (Table 1). The

TABLE 1 Clinical trials for natural compounds or herbal medicines combining with chemotherapy

Recruitment status	Natural compounds	Drugs	Phase	Disease	Trial ID
Clinical trial for natural compound combinations					
Unknown	Curcumin	Gemcitabine Celebrex	III	Pancreatic cancer	NCT00486460
+	+	+	+	Colon cancer	NCT00295035
Clinical trial for herbal products combinations					
Completed	Teng-Long-Bu-Zhong-Tang	Oxaliplatin Capecitabine	II	Colon cancer	NCT01975454
	TCM	Cyclophosphamide Doxorubicin HCl	+	Breast cancer	NCT00028964
	+	Docetaxel Vinorelbine Gemcitabine	+	NSCLC	NCT01780181
	+	Vinorelbine Platinum-based chemotherapy	III	+	NCT01441752
	+	CDDP 5-FU	II	Peritoneal carcinomatosis	NCT02638051
	Jin Fu Kang	Docetaxel	+	NSCLC	NCT00260026
Recruiting	TCM	Adjuvant chemotherapy	+	Breast cancer	NCT03797248
	+	Standard chemotherapy protocols	I	NSCLC	NCT02737735
Enrolling by invitation	Yiqi-yangyin-jiedu decoction	Gefitinib	III	Lung cancer	NCT02929693
Active, not recruiting	PHY906	Sorafenib Tosylate	I	Liver cancer	NCT01666756
Unknown	+	Gefitinib Erlotinib Icotinib	NA	Pulmonary adenocarcinoma	NCT01745302
	+	Lotrozole	NA	Polycystic ovary syndrome	NCT01431352

Note. For detail information about each clinical trial, see following website: https://clinicaltrials.gov/.
Abbreviations: +, The same with above cell; 5-FU, 5-Fluorouracil; CDDP, cisplatin; NA, not applicable; NSCLC, non-small-cell lung cancer; TCM, traditional Chinese medicine.

conventional chemotherapeutic drugs used in these clinical trials include the platinum-based chemotherapeutic drugs (e.g., cisplatin and oxaliplatin), gemcitabine, and docetaxel. These drugs can cause severe side effects during therapy such as nephrotoxicity caused by cisplatin and a high prevalence of haematopoiesis suppression by gemcitabine (Manohar & Leung, 2018; Takei et al., 2017). Although some of the clinical trials were complete, none of the results was reported in detail (Table 1). The aim of this article is to highlight recent preclinical evidence on the potential of natural products as adjuvants in cancer therapy.

2 | HERBAL COMPOUNDS WITH THE POTENTIAL TO SYNERGIZE WITH ANTITUMOR DRUGS

A synergistic effect is described as an increase in efficacy for a combination of components when compared with a single one (Pai, Cottrell, Kashuba, & Bertino, 2015). Data focusing on the toxic episodes of chemotherapy has led to the characterization of novel strategies, including the exploitation of natural compounds in combination therapies. The goals of including natural compounds in cancer chemotherapies are as follows: (a) to widen the therapeutic window of the chemotherapeutic drugs and (b) to decrease the occurrence of chemotherapy resistance (Ouyang et al., 2014). The next section will summarise herbal or folk medicines and natural compounds that act as chemosensitizers, chemoresistance reducers, or chemotherapeutic protectors, in clinical use.

2.1 | Natural compounds acting as chemotherapeutic drug sensitizers

Chemosensitization refers to the potentiation of the tumoricidal effect of chemotherapeutic drugs by other low MW compounds, including making cancer cells more predisposed to chemotherapeutic drugs (Oliveira, Mendes, & Torchilin, 2017). The chemosensitizers can be natural products or synthetic compounds. This section will discuss the naturally sourced chemosensitizers that make cancer cells aware of responding therapeutic agents. Vincristine is a natural alkaloid isolated from *Catharanthus roseus* that is currently used in acute lymphocytic lymphoma and neuroblastoma (Below & Das, 2019). However, due to its high cytotoxicity and narrow therapeutic window, it is restricted for further use, especially in paediatric malignancy (Parasramka, Talari, Rosenfeld, Guo, & Villano, 2017). Bahmani et al. (2018) found that another plant extract from *Centaurea albonitens*, could significantly enhance the cytotoxicity of vincristine against leukaemia cell lines without increasing toxicity to normal cells. To reduce the cardiotoxicity and resistance due to doxorubicin, numerous plant extracts have been used with doxorubicin, in screening synergistic effects. So far, an aqueous extract of *Solanum nigrum* Linn. was shown to potentiate doxorubicin against colorectal cancer and ovarian cancer through autophagy induction (Tai et al., 2013; C. W. Wang et al., 2015). Based on the same idea, polysaccharides isolated from *Agrocybe aegerita* and aqueous extract of *S. nigrum*

Linn. were found to increase cytotoxicity of 5-fluorouracil (5-FU) against oesophageal carcinoma, ovarian cancer, and colorectal cancer via regulating pro-inflammatory cytokine such as TNF-α and IFN-γ (Ji, Zheng, Ye, Wu, & Chen, 2013; Tai et al., 2013; C. W. Wang et al., 2015). For increasing the anti-cancer effects of paclitaxel, three natural phenolic acids (caffeic acid, rosmarinic acid, and ursolic acid) were used with paclitaxel in ex vivo breast cancer cells, and found to promote cytotoxicity these cells by modulating the tumour micro-environment (Carranza-Torres et al., 2015). Such results show that it is possible to increase the cytotoxic effects of known anti-cancer agents, with natural compounds. There are numerous studies focusing on synergism between herbal compounds and cancer therapeutic drugs, both in vitro and in vivo. A large percentage of the natural compounds are flavonoids and phenolics, which implies that flavonoids and phenolics have more potential than other subgroups. However, curcumin is the most studied natural compound (Table 2). These studies cover the most prevalent and fatal cancers, for example, lung cancer, breast cancer, and colorectal cancer. Interestingly, these studies focused on curcumin potentiating chemotherapeutic efficacy (by carboplatin, 5-FU, doxorubicin, and radiation) have shown that curcumin promotes chemotherapy through regulating the expression or activity of the transcription factor NF-κB. This finding implies that curcumin might target upstream signalling modulators of NF-κB or NF-κB itself (Table 2). Most of these herbal enhancers for promoting cytotoxicity of chemotherapeutic agents exert their functions via targeting the stress–stimuli response, that is to oxidative stress and particularly NF-κB, which seems to be an indicator for determining the potency of chemotherapeutic cytotoxicity. When taken together, natural compounds or herbal products have a high potential to support chemotherapeutic drugs to fight cancer cells.

2.2 | Herbal compounds reduce resistance against cancer therapy

Clinically, herbal compounds can reduce resistance against cancer therapies, and this has become a critical concern. Up to now, drug resistance (excluding radiation-resistance) in cancer cells remains the most challenging aspect of cancer treatment, especially in NSCLC and prostate cancer (Chang, 2011; Wade & Kyprianou, 2018). Such resistance in cancers reveals a transformation of cancer cells from drug susceptible to resistant, which leads to higher toxicity and expenditures in treatments (Housman et al., 2014; Zheng, 2017). About 90% of treatment failures in recurrent cancer therapy and 80–90% of cancer death is strongly correlated to cancer resistance (Mansoori, Mohammadi, Davudian, Shirjang, & Baradaran, 2017; Yuan et al., 2017).

Prevailing mechanisms of chemoresistance are classified into seven phases: drug flux, DNA damage repair, cell death inhibition, epithelial-mesenchymal transition (EMT), drug target alteration, drug inactivation, and epigenetics (Housman et al., 2014), and notably, drug flux is the most concerned issue in this topic. Cancer cells pump chemotherapeutic agents out of the cells using the multidrug resistance proteins (MRPs, also known as MDR or the ABCC family of

TABLE 2 Herbal compounds act as an enhancer of cancer therapy

Structure subclass	Natural compound	Chemotherapeutic drug	Cancer	Signal pathway	Reference[a]
Cell death via specific signalling pathway					
Alkaloid	3,3′-Diindolylmethane	Cisplatin	Ovary	**STAT3**/Akt	(Zou, Xu, Li, Zhang, & Fan, 2018)
	Berberine	Radiation	Esophagus	Rad51	(Liu et al., 2011)
	Ethoxysanguinarine	Cisplatin	Lung	CIP2A	(Liu, Ma, Wen, Cheng, & Zhou, 2014)
	Melatonin	+	Liver	NF-κB/AP-2β	(Hao et al., 2017)
	Neferine	Doxorubicin	Lung	**Fas**/ROS	(Poornima, Kumar, Weng, & Padma, 2014)
	Noscapine	Cisplatin	Ovary	HIF-1α	(Su et al., 2011)
	Piperlongumine	Doxorubicin	Prostate	**Carbonyl reductase 1**	(Piska et al., 2019)
Capsaicinoid	**Capsaicin**	Radiation	Prostate	NF-κB	(Venier et al., 2015)
Diarylheptanoid	Curcumin	5-FU	Gastric	NF-κB	(Kang et al., 2016)
	+	Carboplatin	Lung	Akt/NF-κB	(Kang et al., 2015)
	+	+	Breast	FEN1	(Zou et al., 2018)
	+	+	Colorectal	endoG/NF-κB	(Wang, Liu, & Su, 2014)
	+	+	Lymphoma	Rad51, apoptosis-Caspase	(Zhao et al., 2018)
	+	+	Neuroblastoma	Uniquitin	(D'Aguanno et al., 2012)
	+	+	Ovary	c-Myb/STAT3/NF-κB	(Tian, Tian, Qiao, Li, & Zhang, 2019)
	+	Doxorubicin	Gastric	NF-κB	(Yu, Wu, Dai, Yu, & Si, 2011)
	+	Radiation	Prostate	miR-143	(Liu, Li, Wang, & Luo, 2017)
	+	Rhtrail	Breast	**DR5**/**IAP**	(Park, Cho, Andera, Suh, & Kim, 2013)
Diterpenoid	Adenanthin	**1,25 dihydroxyvitamin D3**	Leukaemia	Prx-1/C/EBP	(Wei et al., 2016)
	Cryptotanshinone	Cisplatin	Ovary	**MMP-2** and **MMP-9**	(Jiang et al., 2017)
	+	**Paclitaxel**	Oral	**JAK**/STAT3 e-Cadherin/p53/ β-catenin	(Wang et al., 2017)
Flavonoid	(−)-Epicatechin	Radiation	Pancreas/Glioma	**Chk1**/p21	(Elbaz, Lee, Antwih, Liu, Huttemann, & Zielske, 2014)
	Formononetin	Doxorubicin	Gastric	**HDAC5**	(Liu et al., 2015)
	Icariin	5-FU	Colorectal	NF-κB	(Shi et al., 2014)
	Luteolin	Cisplatin	Bile duct	**PI3K**/Akt/**mTOR**/ SREP	(Lim, Yang, Bazer, & Song, 2016)
	Naringenin	Paclitaxel	Prostate	PI3K/Akt and **MAPK**	(Lim, Park, Bazer, & Song, 2017)
	WYC02	Cisplatin	Multi cancer	ATM	(Wang et al., 2012)
	Quercetin	Rhtrail	Breast	**c-FLIP**/DR5	(Manouchehri, Turner, & Kalafatis, 2018)
	Silibinin	5-FU	Colorectal	PI3K/MAPK/ **CTNNB1**/nanog/ CD44v6	(Patel et al., 2018)
Isoprenoid	**Vitamine K2**	+	Liver	NF-κB	(Zhang et al., 2011)

(Continues)

TABLE 2   (Continued)

Structure subclass	Natural compound	Chemotherapeutic drug	Cancer	Signal pathway	Reference[a]
Macrolide	Elaiophylin	Cisplatin	Ovary	Cathepsin	(Zhao et al., 2015)
Monoterpenoid	Borneol	+	Oesophagus	PI$_3$K/Akt	(Meng et al., 2018)
Organosulfur	Sulforaphane	Doxorubicin	Ovary	SFN, CA IX	(Pastorek et al., 2015)
Phenolic	Anacardic acid	Radiation	Prostate	γ-H2AX	(Yao et al., 2015)
	Caffeic acid	Metformin	Cervix	AMPK/TCA cycle	(Tyszka-Czochara, Konieczny, & Majka, 2017)
	+	+	+	SNAI1/MMP-9	(Tyszka-Czochara, Lasota, & Majka, 2018)
	Capsaicin	Docetaxel	Prostate	PTEN/PI$_3$K/Akt/ mTOR LKB1/AMPK	(Sanchez, Bort, Mateos-Gomez, Rodriguez-Henche, & Diaz-Laviada, 2019)
	Dicoumarol	Doxorubicin	Urinary tract	NADPH quinone oxidoreductase	(Matsui et al., 2010)
	Emodin	Tamoxifen	Breast	Ras/ERK PI$_3$K/mTOR	(Tseng et al., 2017)
Polyyne	Falcarindiol	5-FU	Colorectal	ER stress	(Jin et al., 2012)
Susquiterpenoid	Heteronemin	Cytarabine	Leukaemia	Ras farnesylation	(Saikia et al., 2018)
	β-Eudesmol	Doxorubicin 5-FU	Bile duct	NADPH quinone oxidoreductase	(Srijiwangsa, Ponnikorn, & Na-Bangchang, 2018)
Phytosteroid	Polyphyllin D	Cisplatin	Ovary	18 unique genes	(Al Sawah et al., 2015)
	Tenacigenin B derivative	Paclitaxel	Ovary	Inhibit Cytochrome P450	(Xie et al., 2019)
Stilbenoid	Resveratrol	Cisplatin	Lung	Mitochondrial depolarization	(Ma et al., 2015)
	+	Doxorubicin	Breast	HSP-27	(Diaz-Chavez et al., 2013)
	+	+	+	Carbonyl reductase 1	(Ito et al., 2013)
Tetrahydrofuran	Acetogenin	Doxorubicin	Ovary	Mitochondrial complex I	(Tormo et al., 2003)
Tripyrrole	Prodigiosin	Paclitaxel	+	Survivin	(Ho et al., 2009)
	+	Doxorubicin	Oral	Doxorubicin accumulation	(Lin & Weng, 2018)
Triterpenoid	Brusatol	5-FU	Pancreas	e-cadherin/Twist/ vimentin/NF-κB	(Lu, Lai, Leung, Leung, Li, & Lin, 2017)
Triterpenoid	Celastrol	Cisplatin	Lung	FANCD2	(Wang, Liu, Cheng, & Zhou, 2015)
	+	Tanespimycin	Glioblastoma	P62, Hsp72, Hsp90	(Boridy, Le, Petrecca, & Maysinger, 2014)
Xanthonoid	Formononetin	Metformin	Breast	ERK1/2/Bcl-2	(Xin, Wang, Ren, & Guo, 2019)
Via apoptosis or autophagy					
Alkaloid	Berberine	Sorafenib	Liver	Apoptosis-Intrinsic	(Huang et al., 2018)
	Indole-3-carbinol	Cisplatin	Ovary	+	(Taylor-Harding et al., 2012)
	+	Doxorubicin	Cervix	+	(Adwas, Elkhoely, Kabel, Abdel-Rahman, & Eissa, 2016)
Carotenoid	Bixin	+	Acute leukaemia	Apoptosis	(Santos, Almeida, Antunes, & Bianchi, 2016)
Diarylheptanoid	Curcumin	Cisplatin	Lung	Apoptosis-Intrinsic	(Baharuddin et al., 2016)

(Continues)

TABLE 2 (Continued)

Structure subclass	Natural compound	Chemotherapeutic drug	Cancer	Signal pathway	Reference[a]
	+	+	Oral	Apoptosis-Intrinsic	(Chen et al., 2018)
	+	Sorafenib	Liver	Apoptosis-Intrinsic	(Bahman, Abaza, Khoushiash, & Al-Attiyah, 2018)
Diterpenoid	Crassin	Doxorubicin	Breast	Apoptosis-ROS	(Richards, Vellanki, Smith, & Hopkins, 2018)
	Ent-kaurane-type diterpenoids	+	Liver	Apoptosis	(Pham, Iscache, Pham, & Gairin, 2016)
Flavonoid	Eupatorin	+	Colorectal	Apoptosis-Intrinsic	(Namazi Sarvestani, Sepehri, Delphi, & Moridi Farimani, 2018)
	Phloretin	Cisplatin	Lung	Apoptotic/MMPs	(Ma, Wang, Nan, Li, Wang, & Jin, 2016)
	Salvigenin	Doxorubicin	Colorectal	Apoptosis-Intrinsic	(Namazi Sarvestani, Sepehri, Delphi, & Moridi Farimani, 2018)
Lignan	Enterolactone	+	Breast	Apoptosis	(Di, De Silva, Krol, & Alcorn, 2018)
	Secoisolariciresinol	+	+	+	(Di, De Silva, Krol, & Alcorn, 2018)
Organosulfur	**Lipoic acid**	Temozolomide	Colorectal	Autophagy	(Goder et al., 2015)
	Alyssin	5-FU	Colorectal	Apoptosis-Extrinsic	(Milczarek et al., 2018)
Phenolic	**Embelin**	Photodynamic therapy	Ehrlich	Apoptosis-Intrinsic	(Joy, Nishanth Kumar, Soumya, Radhika, Vibin, & Abraham, 2014)
Phenolic	Nordihydroguaiaretic acid	Cisplatin	Breast	ROS	(Mundhe, Kumar, Ahmed, Jamdade, Mundhe, & Lahkar, 2015)
Phenolic	**Osthole**	+	Lung	Apoptosis-Intrinsic	(Xu et al., 2013)
Sesquiterpenes	Trans-nerolidol	Doxorubicin	Breast	doxorubicin accumulation	(Hanusova et al., 2017)
	β-Caryophyllene oxide	+	+	+	(Hanusova et al., 2017)
	β-Elemene	Cisplatin	Lung/Brain/ Breast/ Cervix/Ovary/ Colorectal	Apoptsis-Intrinsic & Extrinsic	(Li et al., 2013)
Stilbenoid	Resveratrol	Sorafenib	Liver	Apoptosis-Intrinsic	(Bahman, Abaza, Khoushiash, & Al-Attiyah, 2018)
Triterpenoid	Withaferin A	Radiation	Lymphoma	Apoptosis-ROS, Bcl-2	(Yang, Choi, Kim, Choi, & Kwon, 2011)
	Acetyl-11-keto-β-boswellic acid	+	Glioblastoma	Apoptosis-Intrinsic	(Conti et al., 2018)
Xanthonoid	Forbesione	5-FU	Bile duct	Apoptosis-Intrinsic	(Boueroy et al., 2017)
	Gambogic acid	Doxorubicin	Ovary	Apoptosis-ROS	(Wang & Yuan, 2013)
	Kaempferol	Sorafenib	Liver	Apoptosis-Intrinsic	(Bahman, Abaza, Khoushiash, & Al-Attiyah, 2018)
Reducing chemoresistance via specific mechanism					

(Continues)

TABLE 2 (Continued)

Structure subclass	Natural compound	Chemotherapeutic drug	Cancer	Signal pathway	Reference[a]
Alkaloid	Aaptamine	Cisplatin	Embryonal carcinoma	myc, p53, eIF5A hypusination	(Dyshlovoy et al., 2014)
	Demethyloxyaaptamine	+	+	TNF	(Dyshlovoy et al., 2014)
	Isoaaptamine	+	+	myc, p53, TNF	(Dyshlovoy et al., 2014)
	Sinapine	Doxorubicin	Colorectal	FGFR4-FRS2α-ERK1/2	(Guo, An, Feng, Liu, Wang, & Zhang, 2014)
Diarylheptanoid	Curcumin	Cisplatin	Lung	FA/BRCA	(Chen, Li, Jiang, Lan, & Chen, 2015)
	+	+	Ovary	MEG3, miR-214	(Zhang, Liu, Xu, & Li, 2017)
	+	+	+	miR-186	(Tang, Zhang, & Du, 2010)
Flavonoid	Isoliquiritigenin	+	Oral	ALDH1, CD44, GRP78	(Hu, Yu, Hsieh, Liao, Lu, & Chu, 2017)
	Tectorigenin	Paclitaxel	Ovary	Akt/iκB/IKK	(Yang et al., 2012)
	Wogonin	Doxorubicin	Breast	Nrf2	(Zhong et al., 2013)
Lignan	Silybin	+	Colon	GLUT1	(Catanzaro et al., 2018)
Nucleoside	Clitocine	+	Liver	NF-κB	(Sun et al., 2012)
Organosulfur	Sulforaphane	Cisplatin	Ovary	HIF-1α	(Pastorek et al., 2015)
Phenol	Phenylethyl isothiocyanate	+	In vivo	Mcl-1 glutathionylation	(Li et al., 2016)
	Emodin	Doxorubicin	Lung	Anthracycline reductases	(Hintzpeter, Seliger, Hofman, Martin, Wsol, & Maser, 2016)
Steroid	Cucurbitacin b	+	Gastric	CIP2A/PP2A/mTORC1	(Liu et al., 2017)
Triterpenoid	Adcx	Paclitaxel	Liver	Akt/autophagy	(Sun et al., 2017)
	Polyphyllin I	Erlotinib	Lung	IL-6/STAT3	(Lou, Chen, Zhu, Deng, Wu, & Wang, 2017)
Via inhibiting drug efflux					
Alkaloid	Cinchonine	Paclitaxel	Uterine		(Lee et al., 2011)
	Hydrocinchonine	Paclitaxel	Uterine		(Lee et al., 2011)
	Quinidine	+	+		(Lee et al., 2011)
Diarylheptanoid	Curcuminoid	Doxorubicin	Leukaemia		(Xu, Tian, & Shen, 2013)
Diterpenoid	Tanshinone IIA	Doxorubicin	Gastric		(Xu et al., 2018)
Flavonoid	Biochanin A	Daunorubicin	Breast		(Zhang, Sagawa, Arnold, Tseng, Wang, & Morris, 2010)
	Glabridin	Doxorubicin	+		(Qian et al., 2019)
Lignan	Matairesinol	Doxorubicin	Colon		(Su, Cheng, & Wink, 2015)
	+	+	Leukaemia		(Su, Cheng, & Wink, 2015)
Monoterpene	Borneol-peg-np	Paclitaxel	Ovary		(Zou et al., 2017)
Triterpenoid	Maslinic acid	+	Diarthrosis/smooth muscle		(Villar et al., 2014)
	Oleanolic acid	+	+		(Villar et al., 2014)
	Ursolic acid	Doxorubicin	Breast		(Zong, Cheng, Liu, Pi, Liu, & Song, 2019)
Xanthone	Forbesione	Doxorubicin	Bile duct	NF-κB & p-Glycoprotein	(Hahnvajanawong et al., 2014)

(Continues)

TABLE 2 (Continued)

Structure subclass	Natural compound	Chemotherapeutic drug	Cancer	Signal pathway	Reference[a]
	Isomorellin	+	+		(Hahnvajanawong et al., 2014)
Xanthonoid	Mangiferin	+	Breast	p-Glycoprotein, MRP-1, BCRP	(Louisa, Soediro, & Suyatna, 2014)
	Gambogic acid	Multidrugs	Multi-cancer	p-Glycoprotein	(Wang et al., 2013)

Note. Intrinsic: Bcl-2/Bcl-XL/caspase-3, 9; Extrinsic: DR/Bid/caspase-3, 7, 8; +, the same with above cell.
[a]For Reference list, see Data S1.

transporters) and the Hedgehog receptor Patched 1 (protein patched homolog 1, PTCH1), which reduces drug accumulation within cancer cells and, thereby, lower drug efficacy (Amiri-Kordestani, Basseville, Kurdziel, Fojo, & Bates, 2012; Bidet et al., 2012). MRPs, particularly MRP1 (also known as p-glycoprotein, P-gp), are found over-expression in recurrent cancer cells and which over-expression is associated with poor prognosis (Chen et al., 2016; W. Li et al., 2016). PTCH1 is a newly discovered drug efflux transporter also found to be overexpressed in many metastatic cancers (Hasanovic & Mus-Veteau, 2018). In addition to drug efflux, PTCH1 also acts as a receptor in Hedgehog/Gli signalling pathway that activates Smoothened (Smo)/ Gli transduction and leads to growth factor expression (Armas-Lopez, Zuniga, Arrieta, & Avila-Moreno, 2017; Rimkus, Carpenter, Qasem, Chan, & Lo, 2016). Some chemotherapeutic agents specially target growth factor signalling, for example, gefitinib (Iressa®, epithelial growth factor inhibitor), trastuzumab (Herceptin®, HER2/neu inhibitor), and bevacizumab (Avastin®, vascular endothelial growth factor inhibitor; National Cancer Institute, 2002a, 2002b). However, cancer cells turn on EMT, which leads to anoikis resistance and continuous activation of growth factor signalling during cancer invasion (J. Wang et al., 2016). EMT-induced chemoresistance has been identified in several cancer types, including lung cancer, prostate cancer, and breast cancer (Fischer et al., 2015; J. Huang, Li, & Ren, 2015; Wade & Kyprianou, 2018).

Numerous cancer drugs, including platinum-based chemotherapeutic drugs, mitoxantrone, camptothecin, and doxorubicin, belong to the group known as DNA damage agents (Cheung-Ong, Giaever, & Nislow, 2013). Therefore, DNA repairing capacity would directly affect these cancer drugs' effects (Nagel et al., 2017; Sakthivel & Hariharan,

2017). However, Wang et al. have explored the involvement of Wip1, which is an inhibitor of the ATM kinase-mediated DNA repairing system, in cancer resistance of oral squamous cell carcinoma (OSCC). Wip1 activation is thought to potentiate the cytotoxicity of cisplatin against OSCC (L. Wang, Mosel, Oakley, & Peng, 2012). Unexpectedly, a positive correlation between Wip1 expression and cisplatin resistance in OSCC has now emerged (L. Wang et al., 2012). Thus, both positive and negative relationships between DNA repairing mechanisms and chemoresistance have been found and further investigation is needed to clarify the characteristics of DNA repairing mechanisms in chemoresistance. Figure 1 summarizes the above discussion, showing seven mechanisms of chemoresistance proposed, and giving examples of chemotherapeutic drugs affected by particular chemoresistance mechanisms.

Recent studies on the effects of natural compounds against chemoresistance show that they inhibit MDR protein activity or further reduce MDR protein expressions (Turrini, Ferruzzi, & Fimognari, 2014). Table 2 lists these MDR inhibitors and compounds acting through other mechanisms. This Table shows that MDR inhibition accounts for the highest rate. Interestingly, silybin, a natural lignan isolated from *Silybum marianum*, allows doxorubicin to overcome drug resistance in colorectal cancer by inhibiting glucose transporter 1 (GLUT1) expression. GLUT1 expression could be regulated by the Wnt/β-catenin signalling pathway that has been identified as a cisplatin resistance promoter through the ATM-mediated signalling pathway in laryngeal squamous cell carcinoma cells (L. Wang et al., 2019). Eleven different polyoxypregnanes isolated from *Marsdenia tenacissima* can combat doxorubicin resistance in multidrug resistance cancer cell lines via inhibition of ABC transporters (To et al., 2017).
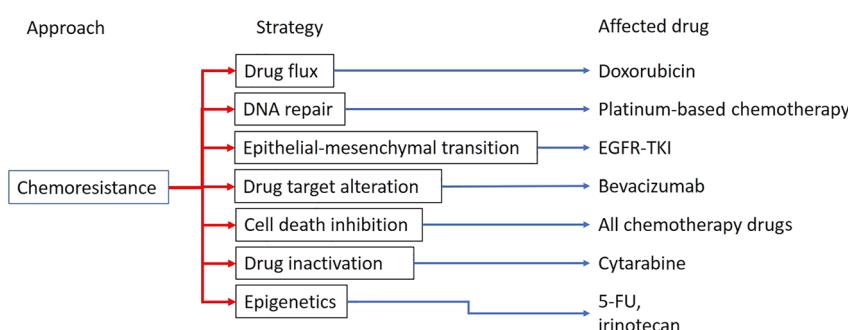
FIGURE 1 Recent-known mechanism of chemoresistance

A series of bisbenzylisoquinoline alkaloids inhibit the transporter P-gp, which leads to high doxorubicin accumulation in MCF-7/ADR breast cancer cell to provide much increased cytotoxicity (Sun & Wink, 2014). Investigation of the antitumor activity of six ergot alkaloids from *Claviceps purpurea*, showed that these ergot alkaloids might bypass chemoresistance mechanisms through unknown signalling pathways in multiple cancers (Mrusek, Seo, Greten, Simon, & Efferth, 2015). Additionally, ellagic acid and resveratrol prevented induction of resistance in ovarian cancer towards cisplatin (Engelke, Hamacher, Proksch, & Kassack, 2016). (Z)-3,4,3′,5′-tetramethoxystilbene, a stilbenoid, increased antitumor efficacy of cisplatin in cisplatin-resistant osteosarcoma cells in in vitro and in vivo (H. Xu, 2016), and another stilbenoid, resveratrol, increased cisplatin uptake and efficacy (Osman et al., 2015). β-Phenylethyl isothiocyanate and 6-gingerol down-regulated intracellular GSH level and concurrently reversed resistance to doxorubicin and cisplatin in resistant-uterine sarcoma cells (Angelini, Conti, Ciofani, Cuccurullo, & Di Ilio, 2013; W. J. Wu et al., 2013). Taken together, the data suggest herbal compounds exert beneficial effects in the treatment of recurrent cancers, when combined with current therapies.

2.3 | Chemopreventive effect of herbal compounds

The non-selective character of most chemotherapeutic drugs usually initiates systemic symptoms as adverse or side effects during therapy (de Oliveira Junior et al., 2018). These adverse effects include cardiotoxicity, nephrotoxicity, hepatotoxicity, and peripheral neuropathy (Duwe et al., 2017; Ma, Kavelaars, Dougherty, & Heijnen, 2018; Santoni et al., 2017; Sharbaf et al., 2017). Sometimes, the adverse effects severely affect the daily quality of life for patients (X. Wu et al., 2016). Many of the adverse effect of chemotherapeutic drugs are caused by the drug itself and its metabolites, usually by inducing ROS formation (Varricchi et al., 2018). Accordingly, a study of doxorubicin metabolism indicated that it was the main cause of doxorubicin-induced cardiomyopathy, through the generation of toxic intermediates and ROS, leadong to the apoptosis of cardiomyocytes (Renu, Abilash, Tirupathi Pichiah, & Arunachalam, 2018). In addition, many naturally sourced antioxidants are present in plant and herbal sources (D. P. Xu

et al., 2017). Therefore, herbal compounds intended to alleviate the adverse effects of chemotherapeutic drugs have been assessed for antioxidation or ROS scavenger effects, in vitro and in vivo. One study in vitro, using cardiomyocytes and doxorubicin indicated that saffron extract could activate Akt/p70s6k and ERK1/2 pathways resulting in decreased cardiomyocytic apoptosis (Chahine, Nader, Duca, Martiny, & Chahine, 2016). In another report focused on irinotecan toxicity, the TCM, Gegen Qinlian decoction, ameliorated gut inflammation by activating the Keap1/Nrf2 pathway and might result in up-regulation of tight junction and down-regulation of inflammatory cytokines (Y. Wu et al., 2019). Other studies have also shown that anthocyanin from black rice tested in vitro with on cardiomyocytes attenuated cardiotoxicity via ERα/β and HSF-1 signalling pathways, and (−)-epigallocatechin gallate (EGCG) reduces NADPH-cytochrome P-450 reductase activity (the key enzyme of doxorubicin toxicity; Dudka et al., 2005; P. C. Huang et al., 2016). In a cell model, indole-3-carbinol and 3,3′-diindolylmethane were cardioprotective in mouse models through the Nrf2/ARE pathway as well (Adwas et al., 2016; Hajra, Basu, Singha Roy, Patra, & Bhattacharya, 2017).

Several herbal compounds including nordihydroguaiaretic acid, eriodictyol-7-O-glucoside, and thymol ameliorated cisplatin-induced renal injury, in vitro and in vivo (Hosseinimehr et al., 2015; Hu, Zhang, Wang, Lou, & Ren, 2012; Mundhe et al., 2015). Resveratrol, genistein, and epigallocatechin-3-gallate attenuated apoptosis of haematopoietic cells via reducing DNA damage (Alotaibi, Bhatnagar, Najafzadeh, Gupta, & Anderson, 2013; Olas & Wachowicz, 2004; Sonaa, Usha, & Ja In, 2013). Again, in photodynamic therapy research, *Pinus halepensis* bark extract prevented the photosensitivity in SCID mice model (Petri et al., 2012). Coniferyl aldehyde, found in wine, reduced radiation damage via phosphorylation of HSF-1 and further increased the activation of ERK1/2 (S. Y. Kim, Lee, Nam, Seo, & Lee, 2015). All these experiments assessed the benefits of the chemoprotective ability of herbal compounds in cancer therapy, derived from a reduction of side effects and a consequent reduction in dose. Nonetheless, drug–herbal interactions, leading to injury may also be important dis-advantages of combination therapy.

TABLE 3 Natural compounds as potential adjuvants to cancer therapy: Unpredictable adverse events

Herbal compounds	Chemotherapeutic drugs	Cancer or normal cell type	Adverse effect and relevant mechanism	Reference[a]
Curcumin	Doxorubicin	Cardiac muscle cells	Apoptosis-ROS	(Hosseinzadeh, Behravan, Mosaffa, Bahrami, Bahrami, & Karimi, 2011)
	Etoposide	Cervix/Breast/Colorectal	Offset cancer cell death via DDR/γ-H2AX	(Saleh, El-awady, Eissa, & Abdel-Rahman, 2012)
Acetyl-L-carnitine	Taxane	Breast cancer	Increase peripheral neuropathy	(Hershman et al., 2013)
Chokeberry	Trabectedin	Liposarcoma	Induce rhabdomyolysis	(Strippoli, Lorusso, Albano, & Guida, 2013)
Bu Zhong Yi Qi Wan	Temozolomide/radiation	Glioblastoma	Induce acute liver toxicity	(Melchardt et al., 2014)

[a]For Reference list, see Data S2.
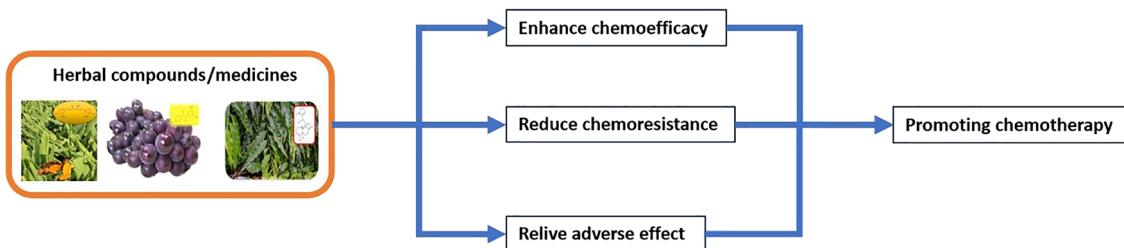
FIGURE 2 Putative mechanism of natural compounds in chemotherapeutic synergism

3 | HERBAL TOXICITIES AND FUTURE REMARKS

An increasing number of cases require closer attention to the additional toxicity induced by the herbal component or by the herbal–drug combination (Table 3). In these examples of herbal-induced drug injury, some popular formulations or compounds are included, such as curcumin and chokeberry, which is usually used for increasing patient stamina to overcome the adverse effects of cancer therapy. A meta-analysis has collected 97 herbal-induced toxicity cases in Korea and found that both single and multiple herbal preparations could induce hepatocellular toxicity, including *Polygonum multiflorum* and *Dictamnus dasycarpus* (W. J. Lee, Kim, Lee, & Son, 2015). A following review collects studies about monoterpene- and susquiterpenes-induced hepatotoxicity and summarize that some common terpenes (e.g. **camphor** and limonene) might injure liver through generating ROS and imparing antioxidant defenses (Zarybnicky, Bousova, Ambroz, & Skalova, 2018). In addition to ROS generation, another hepatotoxic mechanism is simultaneously observed through the modulation of cytochrome P450 (Brewer & Chen, 2017). Coumarins, furanocoumarins, (−)-epigallocatechin-3-gallate, and **piperine** have all demonstrated a potent inhibition of cytochrome P450 isoforms, especially **CYP3A4** which is a key enzyme for oral drug detoxification, and MDRs, which may be inhibited and thus prolong the $t_{1/2}$ of the drug (Brewer & Chen, 2017; Pal & Mitra, 2006; Shamsi, Tran, Tan, Tan, & Lim, 2017). These findings of toxicity from using herbal medicine for cancer therapy suggest that precautions should be taken against the herb-induced or drug-induced liver injury.

Accordingly, the best fit between possible adverse effect and anticancer efficacy is urgently needed in terms of clinical application. The balance between adverse effect and anticancer efficacy can be discussed at two levels, acute and chronic toxicity. Acute toxicity, especially hepatotoxicity, nephrotoxicity, and cardiotoxicity, could be determined during administration. Cardiotoxicity could be measured by left ventricular ejection fraction (LVEF), which directly shows the pumping ability of the heart (Florescu, Cinteza, & Vinereanu, 2013). For hepatotoxicity, clinical criteria of chemotherapy-induced hepatotoxicity is regularly defined by the serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), alkaline phosphatase (ALP), and **γ-glutamyltransferase** (γ-GT) in which increases to 2 or 3 times

higher than the normal upper limit, as acute liver injury is occurring (Y. C. Yu et al., 2017). Nephrotoxicity is defined by serum creatinine level and GFRs (measured by urine volume produced in particular time period) and has five stages from risk to end-stage renal disease (ESRD; Horie et al., 2018). The criteria of biochemical examinations could guide oncologists and researchers to monitor possible toxicities, which can be used to determine the benefits of anticancer efficacy and, subsequently, to proceed or to cease treatment. In practice, a physician could take a more restricted posture towards advancement of ALT and AST levels based on normal ranges, to securely assure the ongoing therapy. Likewise, the above criteria could be applied to monitor the chronic toxicity in liver, heart, and kidney which potent natural compounds/conventional drugs combination could provide greater anticancer efficacy without exceeding about criteria.

Prospectively, the immunostimulatory effect of natural compounds in chemotherapy is a critical issue, as chemotherapy-induced immunosuppression could cause severe opportunistic infections (Galluzzi, Buqué, Kepp, Zitvogel, & Kroemer, 2015). Some natural compounds and herbal products have proved as immunomodulators in vivo, such as Ashwagangha (Withania somnifera) and Brahmi (Bacopa monnieri), which improve **IFN-γ** and **IL-2** expression after LPS exposure (Yamada, Hung, Park, Park, & Lim, 2011). Moreover, the immunomodulating activity of astragaloside (the major components of huang-qi, *Astragalus membranaceus*) has been linked to **CD45** modulation that is essential for T-cell activation (Qi, Gao, Hou, & Wan, 2017; Rheinlander, Schraven, & Bommhardt, 2018; Wan et al., 2013). Combining the immunostimulatory efficacy of herbal products with immunosuppressive chemotherapeutic drugs like gemcitabine, the side effects of immunosuppression might be relieved. Furthermore, these two studies propose a new approach for appraising the enhancement of the potential of natural compounds in combination with chemotherapeutic drugs. Before applying folk, herb, and natural compounds in combination therapy, the antitumor efficacy of folk, herb, and natural compounds needs to be assessed first.

4 | CONCLUSION

Collectively, the mechanisms of natural compounds acting as chemotherapeutic adjuvants could be summarized into three approaches:

directly potentiating tumoricidal effect (sensitizing cancer cells to be more responsive to chemotherapeutic drugs), reversing chemoresistance (diminishing drug efflux or overcoming other mechanism to increase the accumulation of chemotherapeutic drugs in cancer cells), and alleviating toxicity induced by chemotherapeutic drugs (promoting the repairing mechanism in normal cells against damage of chemotherapeutic drugs; Figure 2). After demonstrating anticancer activity as monotherapy, natural compounds could further enhance their application by being chemotherapeutic adjuvants or cooperating drugs in combination therapy. Using TCM or traditional herbal medicine as a chemotherapeutic adjuvant in treating NSCLC or gastric cancer could improve the quality of life of patients, ameliorate myelosuppression, and possibly reduce mortality (Hou et al., 2017; Y. K. Lee, Bae, Yoo, & Cho, 2018; X. Wu et al., 2016). Further studies should look at herbal compounds or low MW compounds that can be applied as an alternative potent supplement for cancer therapy to attenuate any adverse effects and chemoresistance. However, the toxicity of herbal–drug interactions for liver or kidney injury needs to be extensively considered as a precaution during new drug discovery and development.

4.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the UPHAR/BPS Guide to PHARMACOLOGY (Harding et al., 2018), and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18 (Alexander, Christopoulos et al., 2017; Alexander, Cidlowski et al., 2017; Alexander, Fabbro et al., 2017; Alexander, Kelly et al., 2017a, b).

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ORCID

Shian-Ren Lin https://orcid.org/0000-0002-4160-2361
Ching-Feng Weng https://orcid.org/0000-0002-9747-8697

REFERENCES

Adwas, A. A., Elkhoely, A. A., Kabel, A. M., Abdel-Rahman, M. N., & Eissa, A. A. (2016). Anti-cancer and cardioprotective effects of indol-3-carbinol in doxorubicin-treated mice. *Journal of Infection and Chemotherapy*, 22, 36–43. https://doi.org/10.1016/j.jiac.2015.10.001

Alexander, S. P. H., Christopoulos, A., Davenport, A. P., Kelly, E., Marrion, N. V., Peters, J. A., ... CGTP Collaborators (2017). The concise guide to PHARMACOLOGY 2017/18: G protein-coupled receptors. *British Journal of Pharmacology*, 174, S17–S129. https://doi.org/10.1111/bph.13878

Alexander, S. P. H., Cidlowski, J. A., Kelly, E., Marrion, N. V., Peters, J. A., Faccenda, E., ... CGTP Collaborators (2017). The concise guide to PHARMACOLOGY 2017/18: Nuclear hormone receptors. *British Journal of Pharmacology*, 174, S208–S224. https://doi.org/10.1111/bph.13880

Alexander, S. P. H., Fabbro, D., Kelly, E., Marrion, N. V., Peters, J. A., Faccenda, E., ... CGTP Collaborators (2017). The concise guide to PHARMACOLOGY 2017/18: Enzymes. *British Journal of Pharmacology*, 174, S272–S359. https://doi.org/10.1111/bph.13877

Alexander, S. P., Kelly, E., Marrion, N. V., Peters, J. A., Faccenda, E., Harding, S. D., ... CGTP Collaborators (2017a). The concise guide to PHARMACOLOGY 2017/18: Other proteins. *British Journal of Pharmacology*, 174(Suppl 1), S1–S16. https://doi.org/10.1111/bph.13882

Alexander, S. P. H., Kelly, E., Marrion, N. V., Peters, J. A., Faccenda, E., Harding, S. D., ... CGTP Collaborators (2017b). The concise guide to PHARMACOLOGY 2017/18: Transporters. *British Journal of Pharmacology*, 174, S360–S446. https://doi.org/10.1111/bph.13883

Alotaibi, A., Bhatnagar, P., Najafzadeh, M., Gupta, K. C., & Anderson, D. (2013). Tea phenols in bulk and nanoparticle form modify DNA damage in human lymphocytes from colon cancer patients and healthy individuals treated in vitro with platinum-based chemotherapeutic drugs. *Nanomedicine (London, England)*, 8, 389–401. https://doi.org/10.2217/nnm.12.126

Amiri-Kordestani, L., Basseville, A., Kurdziel, K., Fojo, A. T., & Bates, S. E. (2012). Targeting MDR in breast and lung cancer: Discriminating its potential importance from the failure of drug resistance reversal studies. *Drug Resistance Updates*, 15, 50–61. https://doi.org/10.1016/j.drup.2012.02.002

Angelini, A., Conti, P., Ciofani, G., Cuccurullo, F., & Di Ilio, C. (2013). Modulation of multidrug resistance P-glycoprotein activity by antiemetic compounds in human doxorubicin-resistant sarcoma cells (MES-SA/Dx-5): Implications on cancer therapy. *Journal of Biological Regulators and Homeostatic Agents*, 27, 1029–1037.

Armas-Lopez, L., Zuniga, J., Arrieta, O., & Avila-Moreno, F. (2017). The Hedgehog-GLI pathway in embryonic development and cancer: Implications for pulmonary oncology therapy. *Oncotarget*, 8, 60684–60703.

Bahmani, F., Esmaeili, S., Bashash, D., Dehghan-Nayeri, N., Mashati, P., & Gharehbaghian, A. (2018). Centaurea albonitens extract enhances the therapeutic effects of Vincristine in leukemic cells by inducing apoptosis. *Biomedicine & Pharmacotherapy*, 99, 598–607. https://doi.org/10.1016/j.biopha.2018.01.101

Below, J., & Das, J. M. (2019). *Vincristine*. Treasure Island (FL): StatPearls.

Bidet, M., Tomico, A., Martin, P., Guizouarn, H., Mollat, P., & Mus-Veteau, I. (2012). The Hedgehog receptor patched functions in multidrug transport and chemotherapy resistance. *Molecular Cancer Research*, 10, 1496–1508. https://doi.org/10.1158/1541-7786.MCR-11-0578

Brewer, C. T., & Chen, T. (2017). Hepatotoxicity of herbal supplements mediated by modulation of cytochrome P450. *International Journal of Molecular Sciences*, 18, 2353. https://doi.org/10.3390/ijms18112353

Brown, T., Pilkington, G., Bagust, A., Boland, A., Oyee, J., Tudur-Smith, C., ... Dickson, R. (2013). Clinical effectiveness and cost-effectiveness of first-line chemotherapy for adult patients with locally advanced or metastatic non-small cell lung cancer: A systematic review and economic evaluation. *Health Technology Assessment*, 17, 1–278. https://doi.org/10.3310/hta17060

Browning, R. J., Reardon, P. J. T., Parhizkar, M., Pedley, R. B., Edirisinghe, M., Knowles, J. C., & Stride, E. (2017). Drug delivery strategies for platinum-based chemotherapy. *ACS Nano*, 11, 8560–8578. https://doi.org/10.1021/acsnano.7b04092

Carranza-Torres, I. E., Guzman-Delgado, N. E., Coronado-Martinez, C., Banuelos-Garcia, J. I., Viveros-Valdez, E., Moran-Martinez, J., & Carranza-Rosales, P. (2015). Organotypic culture of breast tumor explants as a multicellular system for the screening of natural

compounds with antineoplastic potential. *BioMed Research International*, 2015, 618021.

Chahine, N., Nader, M., Duca, L., Martiny, L., & Chahine, R. (2016). Saffron extracts alleviate cardiomyocytes injury induced by doxorubicin and ischemia-reperfusion in vitro. *Drug and Chemical Toxicology*, 39, 87–96. https://doi.org/10.3109/01480545.2015.1036281

Chang, A. (2011). Chemotherapy, chemoresistance and the changing treatment landscape for NSCLC. *Lung Cancer*, 71, 3–10. https://doi.org/10.1016/j.lungcan.2010.08.022

Chatterjee, K., Zhang, J., Honbo, N., & Karliner, J. S. (2010). Doxorubicin cardiomyopathy. *Cardiology*, 115, 155–162. https://doi.org/10.1159/000265166

Chen, Z., Shi, T., Zhang, L., Zhu, P., Deng, M., Huang, C., ... Li, J. (2016). Mammalian drug efflux transporters of the ATP binding cassette (ABC) family in multidrug resistance: A review of the past decade. *Cancer Letters*, 370, 153–164. https://doi.org/10.1016/j.canlet.2015.10.010

Cheung-Ong, K., Giaever, G., & Nislow, C. (2013). DNA-damaging agents in cancer chemotherapy: Serendipity and chemical biology. *Chemistry & Biology*, 20, 648–659. https://doi.org/10.1016/j.chembiol.2013.04.007

Dudka, J., Jodynis-Liebert, J., Korobowicz, E., Burdan, F., Korobowicz, A., Szumilo, J., ... Murias, M. (2005). Activity of NADPH-cytochrome P-450 reductase of the human heart, liver and lungs in the presence of (−)-epigallocatechin gallate, quercetin and resveratrol: an in vitro study. *Basic & Clinical Pharmacology & Toxicology*, 97, 74–79. https://doi.org/10.1111/j.1742-7843.2005.pto_98.x

Duwe, G., Knitter, S., Pesthy, S., Beierle, A. S., Bahra, M., Schmelzle, M., ... Andreou, A. (2017). Hepatotoxicity following systemic therapy for colorectal liver metastases and the impact of chemotherapy-associated liver injury on outcomes after curative liver resection. *European Journal of Surgical Oncology*, 43, 1668–1681. https://doi.org/10.1016/j.ejso.2017.05.008

Engelke, L. H., Hamacher, A., Proksch, P., & Kassack, M. U. (2016). Ellagic acid and resveratrol prevent the development of cisplatin resistance in the epithelial ovarian cancer cell line A2780. *Journal of Cancer*, 7, 353–363. https://doi.org/10.7150/jca.13754

Fischer, K. R., Durrans, A., Lee, S., Sheng, J., Li, F., Wong, S. T. C., ... Gao, D. (2015). Epithelial-to-mesenchymal transition is not required for lung metastasis but contributes to chemoresistance. *Nature*, 527, 472–476. https://doi.org/10.1038/nature15748

Florescu, M., Cinteza, M., & Vinereanu, D. (2013). Chemotherapy-induced cardiotoxicity. *Maedica (Buchar)*, 8, 59–67.

Galluzzi, L., Buqué, A., Kepp, O., Zitvogel, L., & Kroemer, G. (2015). Immunological effects of conventional chemotherapy and targeted anticancer agents. *Cancer Cell*, 28, 690–714. https://doi.org/10.1016/j.ccell.2015.10.012

Glasgow, M. D., & Chougule, M. B. (2015). Recent developments in active tumor targeted multifunctional nanoparticles for combination chemotherapy in cancer treatment and imaging. *Journal of Biomedical Nanotechnology*, 11, 1859–1898. https://doi.org/10.1166/jbn.2015.2145

Grossi, F., Kubota, K., Cappuzzo, F., de Marinis, F., Gridelli, C., Aita, M., & Douillard, J. Y. (2010). Future scenarios for the treatment of advanced non-small cell lung cancer: Focus on taxane-containing regimens. *The Oncologist*, 15, 1102–1112. https://doi.org/10.1634/theoncologist.2010-0322

Hajra, S., Basu, A., Singha Roy, S., Patra, A. R., & Bhattacharya, S. (2017). Attenuation of doxorubicin-induced cardiotoxicity and genotoxicity by an indole-based natural compound 3,3′-diindolylmethane (DIM) through activation of Nrf2/ARE signaling pathways and inhibiting apoptosis. *Free Radical Research*, 51, 812–827. https://doi.org/10.1080/10715762.2017.1381694

Harding, S. D., Sharman, J. L., Faccenda, E., Southan, C., Pawson, A. J., Ireland, S., ... NC-IUPHAR (2018). The IUPHAR/BPS Guide to PHARMACOLOGY in 2018: Updates and expansion to encompass the new guide to IMMUNOPHARMACOLOGY. *Nucleic Acids Research*, 46, D1091–D1106. https://doi.org/10.1093/nar/gkx1121

Hasanovic, A., & Mus-Veteau, I. (2018). Targeting the multidrug transporter ptch1 potentiates chemotherapy efficiency. *Cell*, 7, E107.

He, Z., Huang, J., Xu, Y., Zhang, X., Teng, Y., Huang, C., ... Sun, W. (2015). Co-delivery of cisplatin and paclitaxel by folic acid conjugated amphiphilic PEG-PLGA copolymer nanoparticles for the treatment of non-small lung cancer. *Oncotarget*, 6, 42150–42168. https://doi.org/10.18632/oncotarget.6243

Horie, S., Oya, M., Nangaku, M., Yasuda, Y., Komatsu, Y., Yanagita, M., ... Muto, S. (2018). Guidelines for treatment of renal injury during cancer chemotherapy 2016. *Clinical and Experimental Nephrology*, 22, 210–244. https://doi.org/10.1007/s10157-017-1448-z

Hosseinimehr, S. J., Asadian, R., Naghshvar, F., Azizi, S., Jafarinejad, M., Noaparast, Z., ... Hosseini, S. A. H. (2015). Protective effects of thymol against nephrotoxicity induced by cisplatin with using 99mTc-DMSA in mice. *Renal Failure*, 37, 280–284. https://doi.org/10.3109/0886022X.2014.991998

Hou, B., Liu, R., Qin, Z., Luo, D., Wang, Q., & Huang, S. (2017). Oral Chinese herbal medicine as an adjuvant treatment for chemotherapy, or radiotherapy, induced myelosuppression: A systematic review and meta-analysis of randomized controlled trials. *Evidence-Based Complementary and Alternative Medicine*, 2017, 3432750.

Housman, G., Byler, S., Heerboth, S., Lapinska, K., Longacre, M., Snyder, N., & Sarkar, S. (2014). Drug resistance in cancer: An overview. *Cancers (Basel)*, 6, 1769–1792. https://doi.org/10.3390/cancers6031769

Hu, Q., Zhang, D. D., Wang, L., Lou, H., & Ren, D. (2012). Eriodictyol-7-O-glucoside, a novel Nrf2 activator, confers protection against cisplatin-induced toxicity. *Food and Chemical Toxicology*, 50, 1927–1932. https://doi.org/10.1016/j.fct.2012.03.059

Huang, J., Li, H., & Ren, G. (2015). Epithelial-mesenchymal transition and drug resistance in breast cancer (Review). *International Journal of Oncology*, 47, 840–848. https://doi.org/10.3892/ijo.2015.3084

Huang, P. C., Kuo, W. W., Shen, C. Y., Chen, Y. F., Lin, Y. M., Ho, T. J., ... Huang, C. Y. (2016). Anthocyanin attenuates doxorubicin-induced cardiomyotoxicity via estrogen receptor-α/β and stabilizes HSF1 to inhibit the IGF-IIR apoptotic pathway. *International Journal of Molecular Sciences*, 17, 1588. https://doi.org/10.3390/ijms17091588

Ji, Y., Zheng, M. F., Ye, S. G., Wu, X. B., & Chen, J. Y. (2013). Agrocybe aegerita polysaccharide combined with chemotherapy improves tumor necrosis factor-α and interferon-γ levels in rat esophageal carcinoma. *Diseases of the Esophagus*, 26, 859–863. https://doi.org/10.1111/j.1442-2050.2012.01397.x

Kim, S. Y., Lee, H. J., Nam, J. W., Seo, E. K., & Lee, Y. S. (2015). Coniferyl aldehyde reduces radiation damage through increased protein stability of heat shock transcriptional factor 1 by phosphorylation. *International Journal of Radiation Oncology, Biology, Physics*, 91, 807–816. https://doi.org/10.1016/j.ijrobp.2014.11.031

Kim, W., Lee, W. B., Lee, J., Min, B. I., Lee, H., & Cho, S. H. (2015b). Traditional herbal medicine as adjunctive therapy for nasopharyngeal cancer: A systematic review and meta-analysis. *Integrative Cancer Therapies*, 14, 212–220. https://doi.org/10.1177/1534735415572881

Kim, W., Lee, W. B., Lee, J. W., Min, B. I., Baek, S. K., Lee, H. S., & Cho, S. H. (2015a). Traditional herbal medicine as adjunctive therapy for breast cancer: A systematic review. *Complementary Therapies in Medicine*, 23, 626–632. https://doi.org/10.1016/j.ctim.2015.03.011

Kuo, Y. T., Liao, H. H., Chiang, J. H., Wu, M. Y., Chen, B. C., Chang, C. M., ... Yen, H. R. (2018). Complementary Chinese herbal medicine therapy improves survival of patients with pancreatic cancer in Taiwan: A nationwide population-based cohort study. *Integrative Cancer Therapies*, 17, 411–422. https://doi.org/10.1177/1534735417722224

Lee, W. J., Kim, H. W., Lee, H. Y., & Son, C. G. (2015). Systematic review on herb-induced liver injury in Korea. *Food and Chemical Toxicology*, 84, 47–54. https://doi.org/10.1016/j.fct.2015.06.004

Lee, Y. K., Bae, K., Yoo, H. S., & Cho, S. H. (2018). Benefit of adjuvant traditional herbal medicine with chemotherapy for resectable gastric cancer. *Integrative Cancer Therapies*, 17, 619–627. https://doi.org/10.1177/1534735417753542

Li, F., & Zhang, N. (2015). Ceramide: Therapeutic potential in combination therapy for cancer treatment. *Current Drug Metabolism*, 17, 37–51. https://doi.org/10.2174/1389200216666151103120338

Li, W., Zhang, H., Assaraf, Y. G., Zhao, K., Xu, X., Xie, J., ... Chen, Z. S. (2016). Overcoming ABC transporter-mediated multidrug resistance: Molecular mechanisms and novel therapeutic drug strategies. *Drug Resistance Updates*, 27, 14–29. https://doi.org/10.1016/j.drup.2016.05.001

Liboiron, B. D., & Mayer, L. D. (2014). Nanoscale particulate systems for multidrug delivery: Towards improved combination chemotherapy. *Therapeutic Delivery*, 5, 149–171. https://doi.org/10.4155/tde.13.149

Lin, S. R., Fu, Y. S., Tsai, M. J., Cheng, H., & Weng, C. F. (2017). Natural compounds from herbs that can potentially execute as autophagy inducers for cancer therapy. *International Journal of Molecular Sciences*, 18, e1412.

Liu, B., Han, L., Liu, J., Han, S., Chen, Z., & Jiang, L. (2017). Co-delivery of paclitaxel and TOS-cisplatin via TAT-targeted solid lipid nanoparticles with synergistic antitumor activity against cervical cancer. *International Journal of Nanomedicine*, 12, 955–968. https://doi.org/10.2147/IJN.S115136

Lorusso, D., Petrelli, F., Coinu, A., Raspagliesi, F., & Barni, S. (2014). A systematic review comparing cisplatin and carboplatin plus paclitaxel-based chemotherapy for recurrent or metastatic cervical cancer. *Gynecologic Oncology*, 133, 117–123. https://doi.org/10.1016/j.ygyno.2014.01.042

Ma, J., Kavelaars, A., Dougherty, P. M., & Heijnen, C. J. (2018). Beyond symptomatic relief for chemotherapy-induced peripheral neuropathy: Targeting the source. *Cancer*, 124, 2289–2298. https://doi.org/10.1002/cncr.31248

Manohar, S., & Leung, N. (2018). Cisplatin nephrotoxicity: A review of the literature. *Journal of Nephrology*, 31, 15–25. https://doi.org/10.1007/s40620-017-0392-z

Mansoori, B., Mohammadi, A., Davudian, S., Shirjang, S., & Baradaran, B. (2017). The different mechanisms of cancer drug resistance: A brief review. *Adv Pharm Bull*, 7, 339–348. https://doi.org/10.15171/apb.2017.041

Mrusek, M., Seo, E. J., Greten, H. J., Simon, M., & Efferth, T. (2015). Identification of cellular and molecular factors determining the response of cancer cells to six ergot alkaloids. *Investigational New Drugs*, 33, 32–44. https://doi.org/10.1007/s10637-014-0168-4

Mundhe, N. A., Kumar, P., Ahmed, S., Jamdade, V., Mundhe, S., & Lahkar, M. (2015). Nordihydroguaiaretic acid ameliorates cisplatin induced nephrotoxicity and potentiates its anti-tumor activity in DMBA induced breast cancer in female Sprague-Dawley rats. *International Immunopharmacology*, 28, 634–642. https://doi.org/10.1016/j.intimp.2015.07.016

Nagel, Z. D., Kitange, G. J., Gupta, S. K., Joughin, B. A., Chaim, I. A., Mazzucato, P., ... Samson, L. D. (2017). DNA repair capacity in multiple pathways predicts chemoresistance in glioblastoma multiforme. *Cancer Research*, 77, 198–206. https://doi.org/10.1158/0008-5472.CAN-16-1151

National Cancer Institute (2002a). *Breast cancer treatment (PDQ(R)): Health professional version*. Bethesda (MD): PDQ Cancer Information Summaries.

National Cancer Institute (2002b). *Non-small cell lung cancer treatment (PDQ(R)): Health professional version*. Bethesda (MD): PDQ Cancer Information Summaries.

Olas, B., & Wachowicz, B. (2004). Resveratrol reduces oxidative stress induced by platinum compounds in blood platelets. *General Physiology and Biophysics*, 23, 315–326.

de Oliveira Junior, R. G., Christiane Adrielly, A. F., da Silva Almeida, J. R. G., Grougnet, R., Thiery, V., & Picot, L. (2018). Sensitization of tumor cells to chemotherapy by natural products: A systematic review of preclinical data and molecular mechanisms. *Fitoterapia*, 129, 383–400. https://doi.org/10.1016/j.fitote.2018.02.025

Oliveira, M. S., Mendes, L. P., & Torchilin, V. P. (2017). Targeted delivery of anticancer drugs: New trends in lipid nanocarriers. In Ficai, A., & Grumezescu, A. M. (Eds.), *Nanostructures for cancer therapy* (pp. 455–484). Philadelphia, United States: Elsevier.

Osman, A. M., Al-Malki, H. S., Al-Harthi, S. E., El-Hanafy, A. A., Elashmaoui, H. M., & Elshal, M. F. (2015). Modulatory role of resveratrol on cytotoxic activity of cisplatin, sensitization and modification of cisplatin resistance in colorectal cancer cells. *Molecular Medicine Reports*, 12, 1368–1374. https://doi.org/10.3892/mmr.2015.3513

Ouyang, L., Luo, Y., Tian, M., Zhang, S. Y., Lu, R., Wang, J. H., ... Li, X. (2014). Plant natural products: From traditional compounds to new emerging drugs in cancer therapy. *Cell Proliferation*, 47, 506–515. https://doi.org/10.1111/cpr.12143

Pai, M. P., Cottrell, M. L., Kashuba, A. D. M., & Bertino, J. S. (2015). 19—Pharmacokinetics and pharmacodynamics of anti-infective agents. In J. E. Bennett, R. Dolin, & M. J. Blaser (Eds.), *Mandell, Douglas, and Bennett's principles and practice of infectious diseases* (Eighth ed.) (pp. 252–262.e252). Philadelphia: Content Repository Only!

Pal, D., & Mitra, A. K. (2006). MDR- and CYP3A4-mediated drug-herbal interactions. *Life Sciences*, 78, 2131–2145. https://doi.org/10.1016/j.lfs.2005.12.010

Parasramka, S., Talari, G., Rosenfeld, M., Guo, J., & Villano, J. L. (2017). Procarbazine, lomustine and vincristine for recurrent high-grade glioma. *Cochrane Database of Systematic Reviews*, 7, CD011773.

Petri, A., Alexandratou, E., Kyriazi, M., Rallis, M., Roussis, V., & Yova, D. (2012). Combination of Fospeg-IPDT and a natural antioxidant compound prevents photosensitivity in a murine prostate cancer tumour model. *Photodiagnosis and Photodynamic Therapy*, 9, 100–108. https://doi.org/10.1016/j.pdpdt.2011.11.002

Qi, Y., Gao, F., Hou, L., & Wan, C. (2017). Anti-inflammatory and immunostimulatory activities of astragalosides. *The American Journal of Chinese Medicine*, 45, 1157–1167. https://doi.org/10.1142/S0192415X1750063X

Renu, K., Abilash, V. G., Tirupathi Pichiah, P. B., & Arunachalam, S. (2018). Molecular mechanism of doxorubicin-induced cardiomyopathy—An update. *European Journal of Pharmacology*, 818, 241–253. https://doi.org/10.1016/j.ejphar.2017.10.043

Rheinlander, A., Schraven, B., & Bommhardt, U. (2018). CD45 in human physiology and clinical medicine. *Immunology Letters*, 196, 22–32. https://doi.org/10.1016/j.imlet.2018.01.009

Rimkus, T. K., Carpenter, R. L., Qasem, S., Chan, M., & Lo, H. W. (2016). Targeting the sonic hedgehog signaling pathway: Review of smoothened and GLI inhibitors. *Cancers (Basel)*, 8, 22. https://doi.org/10.3390/cancers8020022

Sakthivel, K. M., & Hariharan, S. (2017). Regulatory players of DNA damage repair mechanisms: Role in cancer chemoresistance. *Biomedicine & Pharmacotherapy*, 93, 1238–1245. https://doi.org/10.1016/j.biopha.2017.07.035

Santoni, M., Guerra, F., Conti, A., Lucarelli, A., Rinaldi, S., Belvederesi, L., ... Berardi, R. (2017). Incidence and risk of cardiotoxicity in cancer

patients treated with targeted therapies. *Cancer Treatment Reviews*, *59*, 123–131. https://doi.org/10.1016/j.ctrv.2017.07.006

Shamsi, S., Tran, H., Tan, R. S., Tan, Z. J., & Lim, L. Y. (2017). Curcumin, Piperine, and capsaicin: A comparative study of spice-mediated inhibition of human cytochrome P450 isozyme activities. *Drug Metabolism and Disposition*, *45*, 49–55. https://doi.org/10.1124/dmd.116.073213

Sharbaf, F. G., Farhangi, H., & Assadi, F. (2017). Prevention of chemotherapy-induced nephrotoxicity in children with cancer. *International Journal of Preventive Medicine*, *8*, 76. https://doi.org/10.4103/ijpvm.IJPVM_40_17

Sonaa, E., Usha, S., & Ja In, J. (2013). An ex vivo study of selenium, genistein on the morphological and nuclear changes in anticancer drug-induced apoptosis in human peripheral blood lymphocytes. *BioFactors*, *39*, 279–293. https://doi.org/10.1002/biof.1069

Sulthana, S., Banerjee, T., Kallu, J., Vuppala, S. R., Heckert, B., Naz, S., … Santra, S. (2017). Combination therapy of NSCLC using Hsp90 inhibitor and doxorubicin carrying functional nanoceria. *Molecular Pharmaceutics*, *14*, 875–884. https://doi.org/10.1021/acs.molpharmaceut.6b01076

Sun, Y. F., & Wink, M. (2014). Tetrandrine and fangchinoline, bisbenzylisoquinoline alkaloids from Stephania tetrandra can reverse multidrug resistance by inhibiting P-glycoprotein activity in multidrug resistant human cancer cells. *Phytomedicine*, *21*, 1110–1119. https://doi.org/10.1016/j.phymed.2014.04.029

Tai, C. J., Wang, C. K., Tai, C. J., Lin, Y. F., Lin, C. S., Jian, J. Y., … Chang, C. C. (2013). Aqueous extract of Solanum nigrum leaves induces autophagy and enhances cytotoxicity of cisplatin, doxorubicin, docetaxel, and 5-fluorouracil in human colorectal carcinoma cells. *Evidence-Based Complementary and Alternative Medicine*, *2013*, 514719.

Takei, Y., Takahashi, Y., Machida, S., Taneichi, A., Takahashi, S., Nagashima, T., … Fujiwara, H. (2017). Response to and toxicity of gemcitabine for recurrent ovarian cancer according to number of previous chemotherapy regimens. *The Journal of Obstetrics and Gynaecology Research*, *43*, 358–364. https://doi.org/10.1111/jog.13203

To, K. K. W., Wu, X., Yin, C., Chai, S., Yao, S., Kadioglu, O., … Lin, G. (2017). Reversal of multidrug resistance by Marsdenia tenacissima and its main active ingredients polyoxypregnanes. *Journal of Ethnopharmacology*, *203*, 110–119.

Turrini, E., Ferruzzi, L., & Fimognari, C. (2014). Natural compounds to overcome cancer chemoresistance: Toxicological and clinical issues. *Expert Opinion on Drug Metabolism & Toxicology*, *10*, 1677–1690. https://doi.org/10.1517/17425255.2014.972933

Varricchi, G., Ameri, P., Cadeddu, C., Ghigo, A., Madonna, R., Marone, G., … Tocchetti, C. G. (2018). Antineoplastic drug-induced cardiotoxicity: A redox perspective. *Frontiers in Physiology*, *9*, 167. https://doi.org/10.3389/fphys.2018.00167

Volkova, M., & Russell, R. 3rd (2011). Anthracycline cardiotoxicity: Prevalence, pathogenesis and treatment. *Current Cardiology Reviews*, *7*, 214–220.

Wade, C. A., & Kyprianou, N. (2018). Profiling prostate cancer therapeutic resistance. *International Journal of Molecular Sciences*, *19*, 904. https://doi.org/10.3390/ijms19030904

Wan, C. P., Gao, L. X., Hou, L. F., Yang, X. Q., He, P. L., Yang, Y. F., … Zuo, J. P. (2013). Astragaloside II triggers T cell activation through regulation of CD45 protein tyrosine phosphatase activity. *Acta Pharmacologica Sinica*, *34*, 522–530. https://doi.org/10.1038/aps.2012.208

Wang, C. W., Chen, C. L., Wang, C. K., Chang, Y. J., Jian, J. Y., Lin, C. S., … Tai, C. J. (2015). Cisplatin-, doxorubicin-, and docetaxel-induced cell death promoted by the aqueous extract of solanum nigrum in human ovarian carcinoma cells. *Integrative Cancer Therapies*, *14*, 546–555. https://doi.org/10.1177/1534735415588826

Wang, J., Wei, Q., Wang, X., Tang, S., Liu, H., Zhang, F., … Luu, H. H. (2016). Transition to resistance: An unexpected role of the EMT in cancer chemoresistance. *Genes & Diseases*, *3*, 3–6. https://doi.org/10.1016/j.gendis.2016.01.002

Wang, L., Mosel, A. J., Oakley, G. G., & Peng, A. (2012). Deficient DNA damage signaling leads to chemoresistance to cisplatin in oral cancer. *Molecular Cancer Therapeutics*, *11*, 2401–2409. https://doi.org/10.1158/1535-7163.MCT-12-0448

Wang, L., Sun, J., Gao, P., Su, K., Wu, H., Li, J., … Lou, W. (2019). Wnt1-inducible signaling protein 1 regulates laryngeal squamous cell carcinoma glycolysis and chemoresistance via the YAP1/TEAD1/GLUT1 pathway. *Journal of Cellular Physiology*, *234*, 15941–15950.

Wu, L., Leng, D., Cun, D., Foged, C., & Yang, M. (2017). Advances in combination therapy of lung cancer: Rationales, delivery technologies and dosage regimens. *Journal of Controlled Release*, *260*, 78–91. https://doi.org/10.1016/j.jconrel.2017.05.023

Wu, W. J., Zhang, Y., Zeng, Z. L., Li, X. B., Hu, K. S., Luo, H. Y., … Xu, R. H. (2013). β-phenylethyl isothiocyanate reverses platinum resistance by a GSH-dependent mechanism in cancer cells with epithelial-mesenchymal transition phenotype. *Biochemical Pharmacology*, *85*, 486–496. https://doi.org/10.1016/j.bcp.2012.11.017

Wu, X., Chung, V. C., Lu, P., Poon, S. K., Hui, E. P., Lau, A. Y., … Wu, J. C. (2016). Chinese herbal medicine for improving quality of life among nonsmall cell lung cancer patients: Overview of systematic reviews and network meta-analysis. *Medicine (Baltimore)*, *95*, e2410. https://doi.org/10.1097/MD.0000000000002410

Wu, Y., Wang, D., Yang, X., Fu, C., Zou, L., & Zhang, J. (2019). Traditional Chinese medicine Gegen Qinlian decoction ameliorates irinotecan chemotherapy-induced gut toxicity in mice. *Biomedicine & Pharmacotherapy*, *109*, 2252–2261. https://doi.org/10.1016/j.biopha.2018.11.095

Xu, D. P., Li, Y., Meng, X., Zhou, T., Zhou, Y., Zheng, J., … Li, H. B. (2017). Natural antioxidants in foods and medicinal plants: Extraction, assessment and resources. *International Journal of Molecular Sciences*, *18*, 96. https://doi.org/10.3390/ijms18010096

Xu, H. (2016). (Z)-3,4,4′,5′-tetramethoxystilbene, a natural product, induces apoptosis and reduces viability of paclitaxel-and cisplatin-resistant osteosarcoma cells. *Journal of Cancer Research and Therapeutics*, *12*, 1261–1265. https://doi.org/10.4103/0973-1482.158035

Yamada, K., Hung, P., Park, T. K., Park, P. J., & Lim, B. O. (2011). A comparison of the immunostimulatory effects of the medicinal herbs Echinacea, Ashwagandha and Brahmi. *Journal of Ethnopharmacology*, *137*, 231–235. https://doi.org/10.1016/j.jep.2011.05.017

Yu, J., Wang, C., Kong, Q., Wu, X., Lu, J. J., & Chen, X. (2018). Recent progress in doxorubicin-induced cardiotoxicity and protective potential of natural products. *Phytomedicine*, *40*, 125–139. https://doi.org/10.1016/j.phymed.2018.01.009

Yu, Y. C., Mao, Y. M., Chen, C. W., Chen, J. J., Chen, J., Cong, W. M., … Chinese Medical Association (CMA) (2017). CSH guidelines for the diagnosis and treatment of drug-induced liver injury. *Hepatology International*, *11*, 221–241. https://doi.org/10.1007/s12072-017-9793-2

Yuan, R., Hou, Y., Sun, W., Yu, J., Liu, X., Niu, Y., … Chen, X. (2017). Natural products to prevent drug resistance in cancer chemotherapy: A review. *Annals of the new York Academy of Sciences*, *1401*, 19–27. https://doi.org/10.1111/nyas.13387

Zarybnicky, T., Bousova, I., Ambroz, M., & Skalova, L. (2018). Hepatotoxicity of monoterpenes and sesquiterpenes. *Archives of Toxicology*, *92*, 1–13. https://doi.org/10.1007/s00204-017-2062-2

Zhang, Y., Yang, M., Ji, Q., Fan, D., Peng, H., Yang, C., … Zhou, Y. (2011). Anoikis induction and metastasis suppression by a new integrin αvβ3 inhibitor in human melanoma cell line M21. *Investigational New Drugs*, *29*, 666–673. https://doi.org/10.1007/s10637-010-9616-y

Zheng, H. C. (2017). The molecular mechanisms of chemoresistance in cancers. *Oncotarget*, *8*, 59950–59964. https://doi.org/10.18632/oncotarget.19048

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