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A review of the pharmacodynamic effect of chemo-herbal drug combinations therapy for cancer treatment

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Abstract

There is mounting evidence that cancer patients co-administer herbal drugs with chemotherapy, however, information on the pharmacodynamic (PD) effects of such combination therapy is scarce. Natural products including crude extracts, herbal formulas, and bioactive compounds from plants hold great potential to prevent and treat cancers. More importantly, some herbal drugs can reduce the incidence of chemotherapy-induced toxicity including oral mucositis, gastrointestinal toxicity, hepatotoxicity etc. This review focuses on the effectiveness of some herbal products as adjuvant therapy and describes the possible mechanisms of chemo-herbal drug PD interactions in enhancing the efficacy/ or reducing the side effects of chemotherapy. We also highlighted recent advances in preclinical *in vitro* and *in vivo* studies to establish the effectiveness of herbal medicine to efficacy or counteract chemotherapy-induced side effects. In addition, we draw particular attention to the synergistic effects of chemo-herbal drug combination therapy to prevent and treat cancers using evidence from clinical trials. We concluded that herbal drugs hold great potential as adjuvant therapy for the prevention and treatment of chemotherapy-induced side effects. It is important to also highlight that the clinical evidence on chemo-herbal drug combination therapy is limited. There is an urgent need for an in-depth PD evaluation including the safety pharmacology of chemo-herbal drug combination therapy as well as reliable evidence from multicentre clinical trials to establish the beneficial or negative effects of chemo-herbal drug combination therapy in the ongoing fight against cancer.

Keywords: Herbal-drug, Herbal medicine, Pharmacodynamics, Synergistic, Combination therapy.

List of abbreviations

CAM	Complementary or alternative medicine
DDR	DNA damage response
EGCG	Epigallocatechin gallate
ERK1/2	Extracellular signal-regulated kinase
IL-6	Interleukin 6
MDR	Multidrug resistance
NF-κB	Nuclear factor-κB
P-gp	Permeability glycoprotein
PD	Pharmacodynamics
PD-L1	Programmed death ligand-1
PK	Pharmacokinetics
Rg3	Red ginseng 3
ROS	Reactive oxygen species
STAT-3	Signal transducer and activator of transcription 3
xIAP	X-linked inhibitor of apoptosis protein

1. Introduction

Cancer is a complex disease and requires a multifaceted treatment approach. Systemic therapies using FDA-approved drugs remain the mainstream treatment approaches for metastatic cancers. One of the main disadvantages of chemotherapy is that treatment in most cases comes with severe side effects. As most chemotherapeutic drugs target the DNA of cells, the side effects of the therapy are often caused by damage to rapidly dividing cells such as the bone marrow, hair follicles, and the (sub) mucosa of the GI tract [1]. Severe side effects can lead to a decrease in the quality of life of patients thereby resulting in non-

compliance by patients in taking their chemotherapy, and this can lead to drug resistance [2]. Evidence has shown that cancer patients use herbal medicines/ products also often referred to as complementary or alternative medicine (CAM) in combination with chemotherapy. Some of the reasons why most cancer patients opt to use herbal medicine in combination with chemotherapy include relieving the side effects of chemotherapy, while others believe that herbal medicine has several health benefits such as promoting overall health, managing disease symptoms, and improving the function of the immune system [3]. Apart from this voluntary use of herbal products by patients, there is also research into the possibility of including herbal medicines as part of cancer treatment, for the reduction of chemotherapeutic side effects [4].

The concomitant use of herbal medicine with cancer therapy can either lead to pharmacokinetic (PK) or pharmacodynamic (PD) interactions. In contrast to the mounting evidence on the PK interaction of chemo-herbal drug combination therapy, there is a paucity of information on the PD interaction of herbal medicine with anticancer drugs. Pharmacodynamic interactions arise when one drug alters the pharmacological effect of another drug in a combination regimen [5]. These interactions can either be synergistic/additive or antagonistic. Synergistic interactions occur when two or more drugs (or herbs) enhance a pharmacological effect which is greater than the sum of the individual effects of each drug. The enhancement of efficacy allows for decreasing the dose of the chemotherapeutic, leading to reduced incidence of toxicity and resistance [6]. Antagonistic (or opposing) interactions occur when two or more drugs (or herbs) with opposite pharmacological activities are administered concurrently. These activities can either be on a receptor, or a receptor signalling pathway [7]. Although PD interactions may not be as frequently reported or straightforward as PK interactions, they are a significant factor to consider, especially when prescribing drugs or establishing guidelines for the concurrent use of herbal medicine with chemotherapy.

This review aimed to critically review the recent evidence of chemo-herbal drug PD interactions, highlighting the positive synergistic effects of chemo-herbal drug combination therapy to treat cancers. The review also draws particular attention to the effectiveness of herbal medicine in reducing chemotherapy-induced side effects, highlighting some recent evidence from clinical trials on the concomitant use of herbal medicine with chemotherapeutics.

2. Preclinical research demonstrating the synergistic effects of herbal medicine co-administer with chemotherapeutics

Complementary and alternative medicine (CAM) exhibit chemopreventive effects by inhibiting tumour initiation, cell growth, metastasis, or a combination of these stages. Emerging preclinical evidence has

shown that combining CAM with standard chemotherapy can improve treatment outcomes and enhance other health benefits with minimal incidence of toxicity (Table 1).

2.1 Herbal medicine exhibiting synergy with chemotherapy

Resistance to platinum-based chemotherapy is one of the major hurdles in the treatment of various human cancers. A study by Yallapu et al. [8] found significant synergism when a cisplatin-resistant ovarian cancer cell line was treated with curcumin. The authors pre-treated the cells with curcumin to induce chemosensitization then followed by the platinum drug treatment 2 h later. In another study, Park et al. [9] found that co-treatment with curcumin and cisplatin resulted in a greater synergistic effect by activation of caspase-3 and upregulation of phosphor-mitogen-activated protein kinase and phosphor-extracellular signal-regulated kinase1/2 signalling in bladder cancer cell lines. Emerging evidence has shown that curcumin exerts numerous biological effects by targeting several molecular and cellular pathways such as cell death, p53, Akt, mitogen-activating protein kinases (MAPK), microRNAs, and PTEN [10–12]. In a study by Banerjee et al. [13] the authors found that the combined treatment of docetaxel (10 nM) and curcumin (20μM) for 48 h significantly inhibited the proliferation and induced apoptosis in prostate cancer (PC-3) (DU145 and PC3) cells via modulation of COX-2, p53, NF-κB, phospho-Akt, PI3K, and receptor tyrosine kinase (RTK). These molecular targets play pivotal roles in cancer pathogenesis, hence, the ability of curcumin to interfere with such pathways in combination with conventional chemotherapy may provide an alternative treatment option for cancer patients by enhancing therapeutic outcomes and reducing drug resistance.

Epigallocatechin gallate (EGCG) from *Camellia sinensis* extract enhanced the cytotoxicity of 5-fluorouracil in resistant colorectal cancer cells [14]. EGCG enhanced 5-fluorouracil-induced cytotoxicity and inhibited metastasis of the 5-fluorouracil-resistant cells by facilitating apoptosis and restricting the cell cycle. EGCG also suppressed Notch1, Bmi1, Suz12, and Ezh2, and upregulated self-renewing suppressive-miRNAs, miR-34a, miR-145, and miR-200c, which are some of the main pathways targeted in 5-fluorouracil therapy. *In vivo* experiments in the same study confirmed these results, where EGCG therapy inhibited tumour development in a xenograft mouse model.

Gemcitabine is the first-line therapy for metastatic pancreatic cancer which is one of the deadliest malignancies. However, gemcitabine has little impact on median overall survival for patients with metastatic disease [15]. Yu & Chen [16] investigated the synergistic effect of *Rauwolfia vomitoria* extract and gemcitabine for treating pancreatic cancer. The addition of *R. vomitoria* extracts to gemcitabine significantly inhibited cell growth with a dose reduction effect for gemcitabine. The authors also found that

the combination treatment significantly suppressed tumour growth and metastases in an orthotopic pancreatic cancer mouse model. *R. vomitoria* extract reinforces gemcitabine-induced apoptosis by cleavage of caspase-3 and -8 [17]. Caspase-3 cleaves cytoskeletal and nuclear proteins that play a role in maintaining DNA integrity.

Resveratrol is a renowned bioactive compound synthesized by over 70 plant species [18]. Resveratrol possesses numerous biological activities, but the best-known capacity of resveratrol is to act as a potent antioxidant [19,20]. Resveratrol, in combination with clofarabine and 5-fluorouracil, showed prominent synergistic interactions. For instance, the combination of resveratrol and clofarabine resulted in significant inhibitory effects on malignant mesothelioma growth [21]. In the study, the authors demonstrated that adjuvant therapy with resveratrol inhibited cell proliferation and had limited toxicity on healthy mesothelial cells. The study also indicated that the synergy was associated with the inhibition of Specificity protein 1 (Sp1) and several Sp1-regulated gene products. The Sp1 protein is a nuclear transcription factor involved in the expression of various housekeeping genes and is frequently upregulated in cancer cells [21]. Inhibition of this protein often suppresses tumour formation, metastasis and growth.

Preclinical evidence has shown that combining quercetin and cisplatin produced a synergistic effect in malignant mesothelioma cells, the combination therapy inhibited cell proliferation more than cisplatin alone [22]. The authors reported a significant increase in caspase-3 and-9 when treated with quercetin which could be the reason for the synergistic interaction between quercetin and cisplatin since cisplatin also induces caspases-3 and -9 [22]. Co-treatment of astrocytoma cells with temozolomide and quercetin was reported to initiate programmed cell death more effectively than the individual temozolomide treatment [23]. The authors also reported significant apoptosis which was correlated with an increase in caspase-3 expression.

Ursolic acid is a ubiquitous bioactive compound in several medicinal plants, and it is known to suppress various inflammatory and pro-inflammatory signalling cascades [24]. Shan et al. [25] reported that ursolic acid synergistically enhanced the therapeutic outcome of oxaliplatin in colorectal cancer in both *in vitro* and *in vivo* models. The observed synergistic activity reported in the study was associated with the ability of ursolic acid to inhibit multiple kinase pathways including MAPK, P13K/AKT and NF-κB signalling pathways. A similar synergistic effect was observed when ursolic acid and cisplatin were co-administered to cervical cancer cells. In the study, the authors reported that the combination treatment enhance apoptosis and inhibited cell proliferation via suppression of NF- κB p65 [26].

Triptolide from *Tripterygium wilfordii* has been reported for sensitizing breast cancer cells to doxorubicin through increased DNA damage [27]. The study showed that after 3 hours of triptolide exposure, breast cancer cells had an increased sensitivity to doxorubicin. Triptolide enhanced the sensitivity of breast cancer cells to doxorubicin, compared to other chemotherapeutics such as 5-fluorouracil, paclitaxel and mitomycin C. Interestingly, triptolide hindered the DNA damage response (DDR) to DNA double-strand breaks. The DDR consists of several cellular pathways that detect, activate and repair DNA damage. The DDR is essential for the protection of the integrity of the genome and for ensuring genomic stability [28]. Defects in the DDR raise the risk of gene mutation, chromosome abbreviation and genome instability in human tissues and cells and are known to be a crucial factor in the initiation of tumorigenesis. An improved DDR, however, is generally associated with cancer chemotherapy resistance. Thus, by hindering the DDR using triptolide, the breast cancer cells were not able to restore the DNA damage caused by chemotherapeutics [28].

2.2 Herbal medicine exhibiting cell cycle arrest

Cell cycle arrest is an important mechanism in which cells can physically be halted from progression through the normal cell cycle by a chemical agent [29]. One such chemical agent is ginseng, a popular herbal medicine whose bioactive compound ginsenosides have been found to enhance antiproliferative effects when co-administered with chemotherapeutics. In one study, panaxadiol was co-administered with 5-fluorouracil resulting in a significant increase in the efficacy of cell cycle arrest in gastric cancer cells [30]. The authors reported that the ginsenoside panaxadiol enhances efficacy through regulation of the cell cycle transition and induction of apoptosis. In the study, panaxadiol arrests cancer cells at the G1 phase, whereas 5-fluorouracil affects the cells in the S and G2/M phases. The Ginseng species, *Panax ginseng* and 5-fluorouracil both show an affinity for caspase 3 in gastric cancer cells resulting in significant synergistic effects in combination therapy. More in-depth research into the synergistic effect of *P ginseng* and 5-fluorouracil showed enhanced nitric oxide which was identified as another possible mechanism in the inhibition of human cancer cell line BGC323 [30]. Nitric oxide has been found to directly suppresses the growth of cancer cells by inducing G0/G1 phase arrest through the regulation of the Akt signalling pathway. Ginsenosides were also reported to increase nitric oxide production by inducing phosphorylation of endothelial nitric oxide synthase phosphorylation via the ER-mediated PI3-kinase/Akt pathway. Besides, targeting the HER2 and ERK-2 pathways to overcome drug resistance, ginseng showed downregulation of Programmed death ligand 1 (PD-L1) in lung cancer cells [31]. The authors reported that ginsenoside Rg3 inhibited cell growth and reduced resistance to cisplatin in the resistant cells. The researchers also found overexpression of PD-L1 in A549 / DDP cells relative to A549 cells. Ginsenoside Rg3 reduced the PD-L1 expression caused by chemoresistance and restored the cytotoxicity of T cells to cancer cells. NF-κB p65

and Akt are involved in the overexpression of the PD-L1 and inhibited by Rg3. The bioactive compound panaxadiol saponins from Ginseng was reported to possess hematopoietic growth factor-like activity that promotes the proliferation and differentiation of HPCs in cyclophosphamide-induced myelosuppressive mice. This activity was associated with the ability of the bioactive compound to regulate MEK/ERK protein kinases and extracellular signal-regulated kinase protein kinase, C-kit, and GATA-1 transcription factors [32].

The combination of 5-fluorouracil and resveratrol interfered with the phosphorylation of signal transducer and activator of transcription 3 (STAT3) and Akt in human colorectal cancer cells [33]. The dephosphorylation caused less binding to the transcriptionally regulating telomerase reverse transcriptase (hTERT) promoter. Consequently, the lack of binding reduced telomerase activity, which is crucial to maintaining chromosomal stability over repeated cell division. An additional action of the combination of 5-fluorouracil with resveratrol is the inhibition of Akt phosphorylation. Akt is a serine/threonine kinase which plays a crucial role in cell proliferation, migration and survival.

Elucidating the molecular mechanisms of chemo-herbal drug combination therapy has been the major bottleneck hampering the understanding of the synergy and attenuation of chemotherapy-induced side effects in the clinical use of CAM [34]. Recently, Wu et al. [35] established the molecular mechanisms by which the combination of Xiaoji decoction (XJD) and cisplatin exert a high magnitude of apoptosis in non-small cell lung cancer cells both *in vitro* and *in vivo*. The authors revealed that XJD decoction decreased the IncRNA PVT1 and increased the miR1h1a-sp expressions which were the major factors responsible for the synergy and attenuative effects of this combination therapy. More research on the most frequently used herbal products concurrently with chemotherapy is needed to shed light on the molecular mechanisms of the synergy and amelioration of chemotherapy-induced side effects by natural products and develop the best intervention for the clinical use of herbal-drug combination therapy.

Several efforts have gone into generating multiple data to elucidate the underlying mechanisms in the efficacy of herbal-drug combination therapy and to showcase the health benefits of such treatment regimens (Table 1). Although most of these experimental studies have used *in vitro* cell lines or rodent *in vivo* models to explore mechanisms of herbal-drug combination therapy, it is unlikely that data from most of these studies will be predictive of effects in humans. Hence in-depth scrutiny of herbal-drug combination therapy using the idea model including non-human primates and the best platform technology that will generate acceptable data is urgently needed to facilitate the clinical application of herbal-drug combination therapy to combat the ongoing fight against cancer. One such approach is the safety pharmacology evaluation of

chemo-herbal drug combination therapy for cancer. The ICH guidelines S7A define safety pharmacology as tests for essential life-support organs, the central nervous system, the respiratory system, and the cardiovascular system as core battery tests [36]. Safety pharmacology is now increasingly required for the development and clinical trial of new drugs [37]. To date, no studies have evaluated the safety pharmacology of chemo-herbal drug combination therapy for cancer

3. Clinical trials demonstrating the effectiveness of herbal medicine in reducing chemotherapy-induced toxicity and enhancing synergistic effect

Vomiting and nausea are two of the most common side effects associated with chemotherapy. Previous studies have shown some evidence of the PD effect of herbal-drug combination to combat chemotherapy-induced side effects (Table 2). For instance, 6-gingerol (a major active ingredient extracted from ginger) was used as an anti-emetic agent concomitantly with moderately to highly emetogenic chemotherapy in a randomized double-blind placebo-controlled study. In the study, a total of 88 patients were randomized to receive 6-gingerol 10 mg or a placebo, twice a day for 12 weeks. The authors confirmed that 6-gingerol significantly improved the overall complete response rate together with increased appetite and quality of life compared to the standard anti-emetic treatment group [38]. Marx et al. [39] reported similar positive treatment outcomes when a standardized ginger extract was used concomitantly with moderate or highly emetogenic chemotherapy in a double-blind, randomized placebo-controlled trial. The anti-emetic properties of 6-gingerol are associated with its ability to inhibit neurokinin-1, serotonin and chemotherapy-induced trigger zone [38].

The incidence of oral mucositis in cancer patients receiving chemotherapy at standard doses is between 40-60%, and at high doses of chemotherapy, the incidence goes up to nearly 100% [40]. Typically, oral mucositis causes soreness, bleeding, pain, difficulties in swallowing and alteration of taste [41]. This can lead to a severe decrease in the quality of life of patients. *Plantago ovata* was reported to significantly prevent and treat oral mucositis in breast cancer patients receiving chemotherapy regimens including adriamycin in a double-blind, randomized, controlled crossover trial [42]. The prevention and treatment of oral mucositis by *P. ovata* were associated with its anti-inflammatory, antioxidant and anti-allergic, and protective effect on mucous membranes. Deshmukh et al.[43] assessed the effectiveness of ayurvedic drugs to alleviate chemotherapeutic drug toxicity and improve the quality of life of patients with various malignancies at various stages. Four groups of patients were enrolled on the study, of which one group was treated with six rounds of chemotherapy alone, and the second group was treated with Mauktikyukta Kamdudha and Mauktikyukta Praval Panchamruta during treatment with six rounds of chemotherapy. The

third group received treatment with the same herbal drugs, but only after completing the sixth cycle of chemotherapy. The fourth group received additional Suvarnabhasmadi formulation, in combination with the above-mentioned herbal drugs, after the sixth cycle of chemotherapy. The patients were assessed based on the Common Toxicity Criteria. Patients in groups two, three and four all showed a significant increase in quality of life. Moreover, in all three groups that received Ayurvedic medicine, there was a significant improvement in nausea, appetite, constipation and fatigue compared to the control group.

Myelosuppression with leukocytopenia, erythrocytopenia, and thrombocytopenia are the most frequent and serious side effects among cancer patients undergoing chemotherapy. Ginsenoside Rg3 was reported to improve the median survival time and reduce myelosuppression in advanced non-small lung cancer patients receiving first-line chemotherapy during multicentre, large-sample, randomized clinical trials [44].

Oxidative stress and energy metabolism imbalance are frequent occurrences associated with chemotherapy-induced cardiotoxicity. Several herbal products have been shown to ameliorate ischemic myocardial injury and improve heart function when co-administered with chemotherapy. Injection of a Chinese herbal medicine Dan-Hong was reported to restore doxorubicin-induced cardiotoxicity in H9c2 cells by improving energy metabolism and reducing oxidative stress [45]. Wu et al. [46] reported that fermented *Cordyceps sinensis* attenuated doxorubicin-induced cardiotoxicity by inhibiting myocardial hypertrophy and myocardial damage, regulating systolic function and antioxidant enzyme system as well as improving cardiac energy metabolism. *Platycodon gradiflorum* was reported to exhibit cardioprotective effects in early-stage breast cancer patients undergoing anthracycline-based chemotherapy in a randomized control trial [47].

Oxaliplatin has been used extensively as the first-line chemotherapeutic agent for advanced colorectal cancer. However, the incidence of oxaliplatin-induced peripheral neurotoxicity is extremely common among patients between 82-98% [48]. Kono et al. [49] conducted a phase II double-blind randomized, placebo-controlled study in patients with advanced or recurrent colorectal cancer treated with standard FOLFOX regimens in combination with goshajinkigan (n =44) or placebo (n = 45). The authors reported that goshajinkigan (a traditional Japanese herbal medicine) intervention appeared to have an acceptable safety margin and significantly reduces the incidence of neurotoxicity and delays the onset of grade ≥2 neurotoxicities without impairing FOLFOX efficacy.

In a phase-I escalated clinical trial, curcumin (500 mg/day) was administered with docetaxel (100 mg/m2) for seven days in patients with advanced or metastatic breast cancer. The data revealed a promising

biological response in the chemoprevention by reducing carcinoembryonic antigen tumour markers compared to when the drug was used alone [50]. Darvishi et al. [51] reported significant biological activities among breast cancer patients pre-treated with propolis one week before standard chemotherapy compared to the placebo-controlled group. In the study, the Propolis group (n = 26) showed a marked decrease in pro-inflammatory cytokines tumour necrosis factor, interleukin-2 and protein carbonyl (as a biomarker of oxidative stress) compared to the placebo group (n = 24).

4. Factors limiting the clinical application of herbal medicine as adjuvant therapy

There is a surge of interest among cancer patients to use herbal medicine concurrently with chemotherapy treatment either for its anticancer properties or as supportive care. However, the effectiveness of chemo-herbal drug combination therapy is not well-documented as more studies are urgently needed. Another factor hindering the clinical application of chemo-herbal drug combination therapy is the poor bioavailability of herbal drugs. For instance, resveratrol studies show limited clinical applications due to rapid metabolism being critically below the therapeutical relevant level in the bloodstream, despite showing extremely promising antiproliferative effects in preclinical studies [52–54]. Similarly, curcumin as one of the most popular herbal medicines is faced with the problem of poor absorption, rapid metabolism and systemic elimination culminating in its poor bioavailability thereby limiting its clinical applications [55]. In summary, several factors have been identified as limiting factors hampering the translation of preclinical data into the clinical application of herbal medicine as adjuvant therapy:

1. Lack of quality control and standardization of herbal medicine.
2. Poor bioavailability of herbal drugs.
3. Herbal product contains multi-ingredients with inherent complexity in their interactions with other molecules.
4. Cell line models employ in *in vitro* assays lack tumour microenvironment.
5. The human body is complex compared to animal models frequently used in preclinical studies.
6. Need for an in-depth, high-content screening platform technology including safety pharmacology to elucidate unknown molecular mechanisms by which herbal medicines produce a synergistic effect/ or ameliorate chemotherapy-induced toxicity.
7. Lack of high-quality, multicentre clinical trials to assess the effectiveness of herbal medicine to attenuate the chemotherapy-induced side effects and improve efficacy.

5. Conclusion

This review highlights efforts into understanding the mechanisms behind PD interactions of herbal-drug combination therapy. Several studies have shown the great potential of herbal products as adjuvant therapy to enhance synergy, reduce chemotherapy-induced toxicity, suppressed drug resistance, provides quick drug action, and enhance the quality of life of patients. Recent research has exploited the use of modern platform technology including *in vitro* and *in vivo* experiments to elucidate the benefits/ or risks of herbal-drug combinatory therapy to treat cancer. However, there is a limited corresponding outcome in clinical trials, thus, patients must be cautious in the use of herbal-drug combination therapy for cancer treatment. Also, clinical trials reported in this review are mostly from Asia, hence there is a need for more reliable evidence from other parts of the world to provide a global perspective on herbal-drug combination therapy in the management of cancer. Further studies using high-level platform technology including safety pharmacology as well as multicentre clinical trials are urgently needed to elucidate the risks and benefits of some of the prominent herbal drugs used concurrently with chemotherapeutics.

6. Expert opinion

The safety of chemo-herbal drug combination therapy is now a major concern for both health authorities and the public. Hence, safety pharmacology evaluation of chemo-herbal drug combination therapy is urgently needed to elucidate any undesirable pharmacodynamic effect of such combination therapy. Preclinical evidence has shown that chemo-herbal drug combination therapy enhances therapeutic efficacy through various mechanisms such as inducing apoptosis, reducing cell proliferation, cell cycle arrest as well as interfering with relevant gene expression and protein signalling pathways in various cancer cell lines. However, it is important to highlight that the data from some of the preclinical studies lack translational applications in the clinical use of chemo-herbal drug combination therapy for cancer. To overcome these limitations, firstly, there is a need for an in-depth mechanistic evaluation of chemo-herbal drug combination therapy by adopting advanced methods including network-based approach optimization using state-of-the-art facilities that will generate efficient and reliable data predictive in humans. Secondly, high-level platform technology including safety pharmacology tests as well as multicentre clinical trials are urgently needed to fast-track the adoption of chemo-herbal drug combination therapy for cancer treatment. All these efforts should be geared toward bridging the gap between experimental data and the clinical application of herbal drugs as adjuvant therapy in the management of cancer.

7. Authors' contributions: AO conceptualized the research ideal, ML and CH gather the data, AO prepared the manuscript, RH improved the narrative. All authors have read and approved the last version of the manuscript.

8. Conflict of interest: None

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Table 1. Preclinical evidence of herbal medicine attenuates chemotherapy-induced side effects and exerts synergistic activity

Herbal product	Chemotherapy	Malignancy	Mechanisms of action	Cell line/ animal model	Reference
Scutellaria baicalensis Georgi	Cisplatin	Lewis lung carcinoma (LLC)	Induced apoptosis and Inhibited tumour growth both *in vitro* and *in vivo*. Also, attenuates chemotherapy-induced cachexia and acute kidney injury in a mouse model	LLC Cell line and C57BL/6J mouse model	[56]
23-Hydroxybetulinic acid from *Pulsatilla chinensis* (Bunge) Regel	Doxorubicin	Multiple cancer cell lines	Improve the sensitivity of the tumour cells to doxorubicin through increasing intra-tumour doxorubicin concentration and inhibiting doxorubicin-induced up-regulation of P-gp in the tumour.	Cell line and ICR mice bearing 180 carcinoma tumours	[57]
Moringa oleifera	5-fluorouracil, Cyclophosphamide	Hepatocarcinoma sarcoma	Suppressed hepatocarcinoma sarcoma and improved body weight	Mouse model	[58]
Morinda citrifolia	Cisplatin	NIH-3T3 cells sensitive to sarcoma virus and leukaemia virus propagation	Exhibited cytoprotective effects against normal cells and attenuated cardiac injury in a mouse model	NIH-3T3 cell line	[59]
Huang-Lian-Jie-Du-Tang	Cinnamaldehyde	Human hepatoma cells	Induce mitochondria-medicated and death receptor-mediated apoptosis	Hep G2 cell line	[60]

Salvia miltiorrhiza Bunge	Oxaliplatin	glioblastoma	Relieve acute chemotherapy-induced neuropathic pain	Mouse model	[61]
Shenmai injection (Red ginseng and *Radix ophiopogonis*)	Adriamycin, Paclitaxel and 5-fluorouracil	Colorectal carcinoma	Enhance efficacy by increasing the plasma concentration of chemotherapy	Colon cancer xenograft models	[62,63]
BP10A herbal formular (*Descurainiae sophia* and *Peucedani praeruptorum*)	Oxaliplatin and irinotecan	Colon carcinoma	Significantly decrease tumour growth by inhibiting the Ki-67 expression for tumour cell proliferation and CD31 for angiogenesis.	Patients-derived xenograft model	[64]
Gegen Qinlian decoction (Radix Puerariae, Radix Scutellariae, *Coptis chinensis* and *Radix Glycyrrhizae Praeparata*)	Irinotecan	Colorectal carcinoma	Ameliorate gut toxicity induced by chemotherapy, and significantly inhibit tumour growth by decreasing the levels of pro-inflammatory cytokines.	HT-29 colon cancer cells xenograft	[65]
Polyoxypregnanes (*Marsdenia tenacissima*)	Paclitaxel	Colon and breast cancers	Restored chemosensitivity in ABCB1-overexpressing cancer cells via inhibition of ABCB1 efflux activity.	SW620, HEK293, MDA435/LCC6 and MDA435/LCC6 MDR1 cell lines and xenograft models	[66]
Marsdeniae tenacissimae	Paclitaxel and gefitinib	Leukaemia and lung cancer	Sensitive various cell lines to chemotherapies significantly inhibited tumour growth in mouse models.	H460 and H197 (lung), KB-3-1, HeLa, HepG2 and K562 (leukaemia) cell lines and xenograft mouse models.	[67,68]
Calycosin and Formononetin (*Astragalina alpestris*)	Temozolomide	Brain	Inhibited proliferation and migration of glioma cells and promote apoptosis by upregulating caspase-3 and-9	Glioma cell line and xenograft	[69]

Propolis	5-fluorouracil	Colorectal carcinoma	Reduced aberrant crypt foci (ACF) were counted and the pathological lesions in the distal colonic epithelial tissue. It also reduced the expression of Cox-2, iNOS, and β-catenin proteins.	Mouse xenograft	[70]
Resveratrol	Temozolomide	Brain	Induced apoptotic cell death and cytoprotective autophagy through ROS burst and extracellular signal-regulated kinase	Cell line and xenograft mouse models	[71]
Curcumin	Paclitaxel	Breast	Increased drug accumulation in tumour cells and decreased tumour growth	Xenograft mouse model	[72]
Xanthorrhizol	Tamoxifen	Breast	Significantly decreased tumour volume by increasing protein expression of P38 and P27	MCF-7 xenograft mouse model	[73]
Sijunzi decoction (*Panax ginseng* and *Glycyrrhiza uralensis*)	Cisplatin	Lung	Attenuated cisplatin-induced toxicity, increased the levels of myogenic proteins such as myosin heavy chain and myogenin and decreased atrogin-1	Xenograft mouse model	[74]
Quercetin	Cisplatin	Oral	Promotes cisplatin-induced apoptosis by inhibiting the phosphorylation Akt and IKKβ thereby suppressing the NF-κB and anti-apoptotic protein xIAP	Tca-8113 and SCC-15 cell lines	[75]
Orange peel extract	Doxorubicin	Oesophagal cancer	Orange peel extract intervention protects against cellular toxicity of doxorubicin in vitro by decreasing cellular apoptosis	XTT xenograft model	[76]

			of ESCC CSCs genes. In vivo model revealed that the orange peel extract intervention significantly reduced the tumour size, systemic toxicity, and oxidative stress.		
Shengbai decoction	Cyclophosphamide	Melanoma	Significantly alleviated histopathological damage, and reduced tumour growth and the concentrations of IL-6, IFN-γ and TNF-α in serum. The combination treatment also enhanced the expression of NF-κB and promoted apoptosis compared with Cyclophosphamide alone.	B16F10 tumour-bearing mouse model	[77]
QHF formula (Cinobufotalin, Ginsanoside Rg3, Notoginseng and lentinan)	Cisplatin	Hepatocellula carcinoma	Significantly enhance apoptosis, increased the proportion of cells in the G_0/G_1 phase and decreased the cell proportion in the S-phase. QHF intervention significantly inhibited the growth of tumours and prolong the survival time of mice.	H22 cell mouse model	[78]

Table 2. Clinical evidence of herbal medicine ameliorates chemotherapy-induced toxicity and enhances the efficacy

Name/ ingredient	Dose		Malignancy	Patients (Treatment group/ control group)	Effect/Mechanism	Reference
	Herbal drug	chemotherapy				
Xiaoaiping injection (*Marsdenia tenacissima*)	1 dose/day for 10 days	Platinum-based (Standard dose)	Non-small cell lung cancer and gastric cancer	70/70	Reduced chemotherapy-induced thrombocytopenia by Significantly improved platelet count.	[79]
Curcumin	300 mg, once per week	Paclitaxel (80 mg/m^2)	Breast cancer	75/75	Increased objective response rate and physical performance after 12 weeks. Possibly reducing fatigue.	[72]
MB-6 (fermented soybean extract, green tea extract, Antrodia camphorata mycelia, spirulina, grape seed extract, and curcumin extract)	NS	leucovorin/5-fluorouracil (Standard dose)	Colorectal	72	No significant difference in the best overall response rate and overall survival between the 2 groups. The MB-6 intervention significantly lowered the disease progression rate and reduced the incidence of adverse events	[80]
Ginger extract	160 mg/per	Cisplatin (>50 mg/m2)	Lung (49%) and head and neck cancer (HNC; 35%)	121/123	No differences were reported in terms of safety profile or compliance. The benefit of ginger intervention was recorded among female patients in Functional Living Index	[81]

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					Emesis nausea score differences (day 6–day 1). Rikkunshito intervention significantly lower the incidence of symptoms such as nausea, anorexia, and vomiting and QOL was also enhanced compared to the control group.	[82,83]
Rikkunshito (JP Atractylodes Lancea Rhizome, Ginseng, Pinellia Tuber, Poria Sclerotium, Jujube, Citrus Unshiu Peel, Glycyrrhiza, and Ginger)	2.5 g three times a day	CDDP 10/body i.v. on day 1-5, 5-FU 370 mg/m^2 on day 1-5 and docetaxel 25 mg/m^2 on day 1 and 8.	Oesophagus cancer	8/10		
		Cisplatin	Gastric cancer	5/5		
Hangeshashinto	NS	Cisplatin and docetaxel	Head and neck cancer	40/40	Effectively ameliorate oral mucositis induced by chemoradiation compared to the control. Also, improved completion rates of chemoradiation treatments with cisplatin	[84]
Goshajinkigan	2.5 g orally 3 times daily	mFOLFOX6 plus oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2 and 5-FU 2400 mg/m^2	Colorectal cancer	29/44	Goshajinkigan intervention prevented exacerbation of oxaliplatin-induced peripheral neuropathy but no significant difference in time to treatment failure and severe adverse events between	[85]

NS = Not specified; QOL = Quality of life.