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Opportunities and challenges for co-delivery nanomedicines based on combination of phytochemicals with chemotherapeutic drugs in cancer treatment

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ABSTRACT

The therapeutic limitations such as insufficient efficacy, drug resistance, metastasis, and undesirable side effects are frequently caused by the long duration monotherapy based on chemotherapeutic drugs. multiple combinational anticancer strategies such as nucleic acids combined with chemotherapeutic agents, chemotherapeutic combinations, chemotherapy and tumor immunotherapy combinations have been embraced, holding great promise to counter these limitations, while still taking including some potential risks.

Nowadays, an increasing number of research has manifested the anticancer effects of phytochemicals mediated by modulating cancer cellular events directly as well as the tumor microenvironment. Specifically, these natural compounds exhibited suppression of cancer cell proliferation, apoptosis, migration and invasion of cancer cells, P-glycoprotein inhibition, decreasing vascularization and activation of tumor immunosuppression. Due to the low toxicity and multiple modulation pathways of these phytochemicals, the combination of chemotherapeutic agents with natural compounds acts as a novel approach to cancer therapy to increase the efficiency of cancer treatments as well as reduce the adverse consequences. In order to achieve the maximized combination advantages of small-molecule chemotherapeutic drugs and natural compounds, a variety of functional nano-scaled drug delivery systems, such as liposomes, host–guest supramolecules, supramolecules, dendrimers, micelles and inorganic systems have been developed for dual/multiple drug co-delivery. These co-delivery nanomedicines can improve pharmacokinetic behavior, tumor accumulation capacity, and achieve tumor site-targeting delivery.

In that way, the improved antitumor effects through multiple-target therapy and reduced side effects by decreasing dose can be implemented. Here, we present the synergistic anticancer outcomes and the related mechanisms of the combination of phytochemicals with small-molecule anticancer drugs. We also focus on illustrating the design concept, and action mechanisms of nanosystems with co-delivery of drugs to synergistically improve anticancer efficacy. In addition, the challenges and prospects of how these insights can be translated into clinical benefits are discussed.

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Contents

1. Introduction

In recent decades, although we have made significant progress in cancer treatment, the incidence and mortality of cancer are still among the highest in the world. Worldwide, an estimated 19.3 million new cancer cases and nearly 10.0 million cancer deaths occurred in 2020 [1]. To successfully cure cancer and completely control the development of advanced cancer diseases is still a major problem and challenge. Past studies have shown that most cancers are caused by factors such as genetic disorders, environment, nutrition, and metabolic stress [2].

The Food and Drug Administration (FDA) has already approved more than 300 chemotherapeutic agents, such as nivolumab, ipilimumab, pembrolizumab, 5-flurouracil (5-FU), Olaparib, taxol, vinca alkaloids as well as their derivatives, gemcitabine, methotrexate. Currently, most of the chemotherapeutic drugs used in the clinic are aimed at single targets of nucleic acids, proteins and carcinogenic signaling pathways. For example, platinum drugs

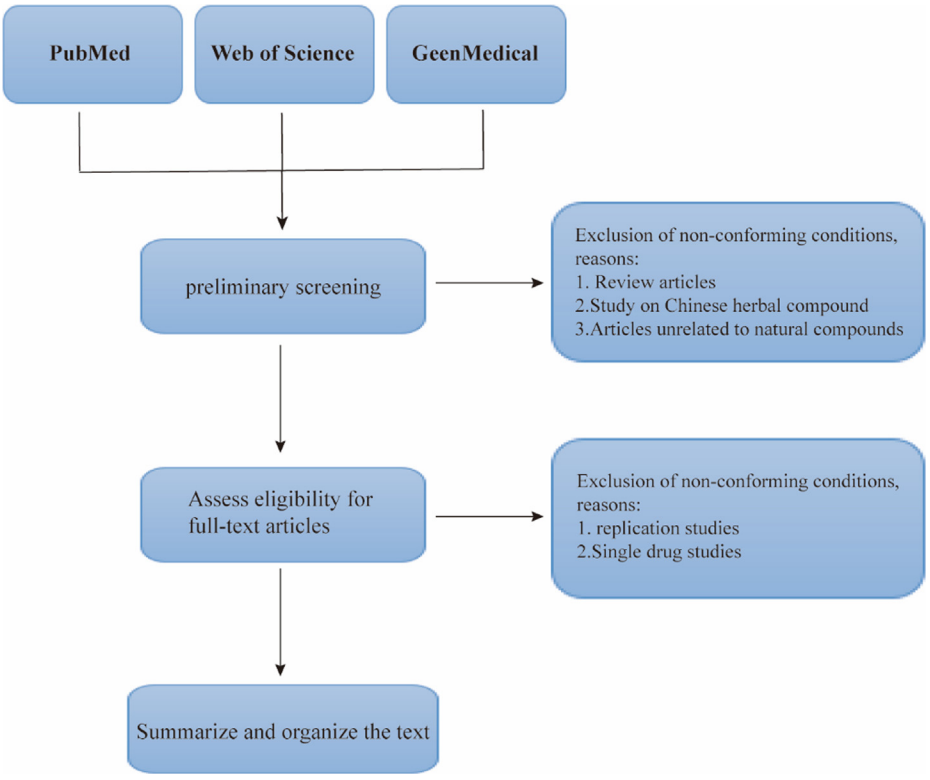

Fig. 1. Study flow diagram.

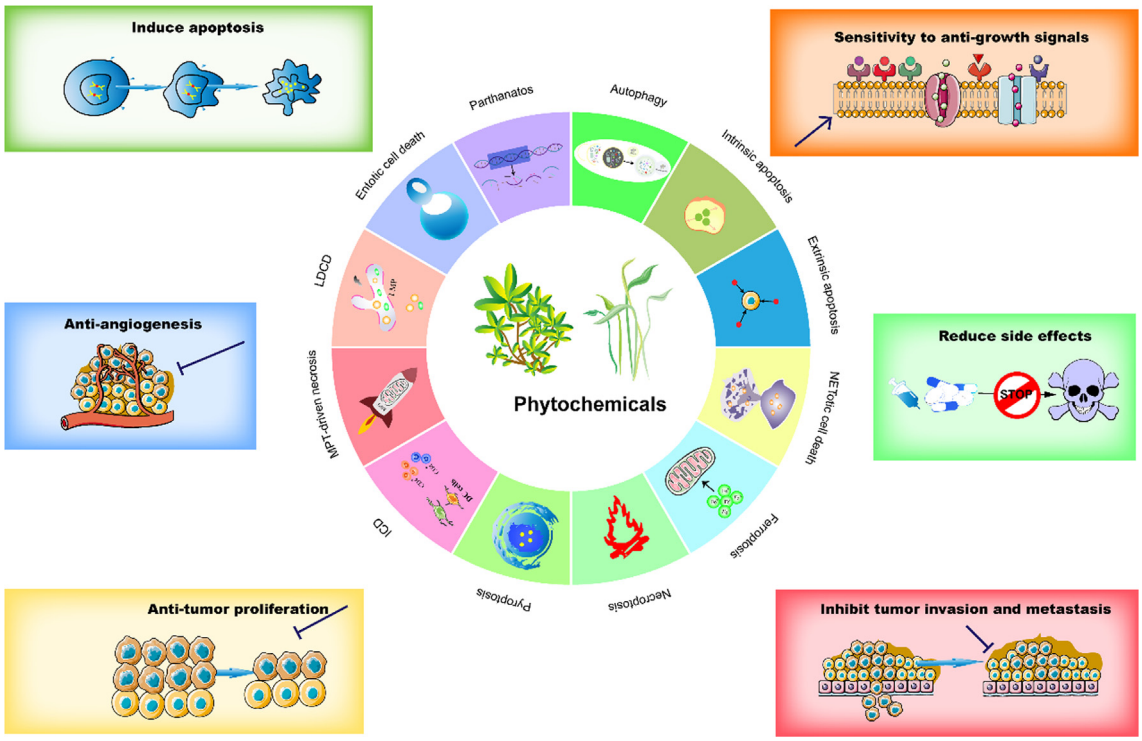

Fig. 2. Various death forms through which phytochemicals induce cancer cells and Mechanism of action.

(oxaliplatin, carboplatin, cisplatin) interfere with the synthesis and metabolism of nucleotides and cause DNA damage. Gefitinib, erlotinib, and icotinib target the tyrosine kinase target. Bevacizumab, sunitinib, and sorafenib inhibit angiogenesis. Even though we have developed hundreds of drugs for cancer treatment, cancer is an evolutionary process. When we give drug interventions, the

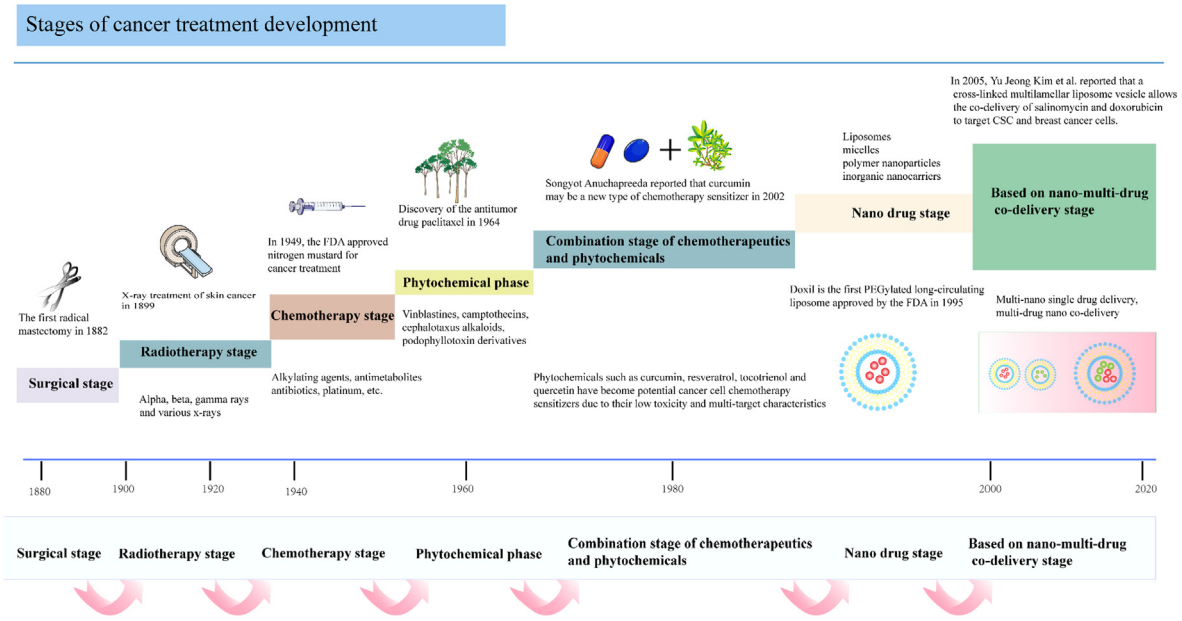

Fig. 3. Stages of co-delivery nanomedicines based on combination of phytochemicals with chemotherapeutic drugs in cancer treatment development.

tumour cells gradually adapt to the changing environment, similar to Darwin's theory of natural selection, which leads to further tumour development [3,4].

So we have to find new drugs to treat this kind of resistance. Coupled with the toxicity and non-targeting of these conventional chemotherapeutics, the treatment of cancer has been greatly restricted. In more recent years, phytochemicals have attracted many people's interests as new treatment options for the development of chemoprevention and cancer treatment. Since most of the established anti-cancer drugs are mostly derived from natural substances, we focused our attention on phytochemicals. The extracts of most natural products have shown good anti-cancer activity, with multiple targets and mild effects, which gives us more choices in the treatment of cancer. For example, baicalin, magnolol, evoline, quercetin, erianin, honokiol, thymoquinone (TQ), shikonin, elemene, tocotrienol (T3), gambogic acid, triptolide [5,6], piperine, resveratrol, tetramethylpyrazine [7], SFN, and ursolic acid affect the development of malignant tumors in many ways [8,9]. By down-regulating oncogenes and up-down suppressor genes, they promote cell apoptosis and autophagy. A variety of death methods such as pyrolysis, necrosis, ferroptosis, etc., induce the growth cycle of cancer cells to stagnate, promote their senescence, inhibit tumor angiogenesis and EMT pathways and other ways to inhibit the development of cancer [10] (Fig. 2). Honokiol can effectively prevent the growth of a multiple of tumors, this phytochemical is able to regulate diverse molecular targets [11,12]. Resveratrol is a non-flavonoid polyphenol, which has the effects of anti-tumor cell proliferation, metastasis, epigenetic changes and inducing cell apoptosis, as well as increasing sensitivity to chemotherapeutics [13]. phytochemicals erianin exerts its anti-cancer effects by inhibiting cell migration and inducing Ca^{2+}/CaM-dependent ferroptosis [14].

Due to the many limitations in the application of chemotherapy drugs, chemotherapy sensitization is a good strategy to break this limitation. This strategy is to use chemotherapy drugs in combination with another or more drugs to overcome their tumor effects. The choice of sensitizing drugs should have low toxicity and multi-targets, which can enhance the sensitivity of cancer cells to chemotherapy drugs through inhibiting signaling pathways involved in chemotherapy resistance. Phytochemicals have shown the potential to play this role in many ways. Numerous research findings have illustrated that the combination of chemotherapeutic drugs and phytochemicals can achieve synergistic sensitization, reverse drug resistance, and reduce the toxicity burden and side-effects of chemotherapeutic drugs [15]. In terms of mechanism, the development of chemotherapy resistance includes the reduction of drug uptake by tumor cells, the activation of DNA repair mechanisms, the abnormal expression of drug-resistant proteins, as well as the overexpression of transporters that causes increased drug outflow. The phytochemicals we take can make up for this defect to a certain extent and raise the effectiveness of chemotherapeutic drugs [15,16]. For example, combined with sulforaphane can reduce the dose of CIS or 5-FU, and at the same time enhance the cytotoxicity of these drugs to HNSCC-CSC, with minimal impact on normal cells [17]. Curcumin combined with anticancer drugs to treat glioblastoma multiforme (GBM) cells reduces their self-renewal, differentiation and malignant properties [18].

Despite the advantages of combination therapy over monotherapy, clinical outcomes remain suboptimal. At the same time, we should consider the clinical feasibility of the combined treatment plan we have adopted, such as the water solubility and bioavailability of drugs, the targeting drugs, and the duration of drugs at the tumor site [19]. Nanomedicine, a drug delivery system with a size of 1–1000 nm, is mainly used to improve the balance between the efficacy and toxicity of combined or embedded chemotherapeutic drugs. Therefore, based on nano-carriers, jointly deliver chemotherapeutic drugs and phytochemicals to the tumor site to reach the purpose of precise treatment. Combined anti-cancer therapy based on nano-drugs can synergistically improve the anti-tumor effect through multi-target therapy, reduce the dosage of each therapeutic agent and reduce side effects [20]. Development of liposomal nanocarriers, which have highly encapsulated hydrophobic flavonoid apigenin to enhance the effect of chemotherapy [21]. HA-DOX-STS-lipo accumulates more as well as improves anti-tumor efficacy in MDA-MB-231 xenograft tumor models that express high levels of CD44 [22]. Nanovesicles have natural cell targeting ability by maintaining the topological structure of plasma membrane proteins. Nanovesicles loaded with chemotherapeutic drugs can enter tumor tissues and reduce tumor growth [23]. Nano-drug co-delivery is the co-delivery of two or

more therapeutic agents in a single nano-carrier system. Two or more drugs are loaded into a single nano-carrier at the same time, which may synchronize the biodistribution and pharmacokinetics of different drugs. So as to achieve a synergistic effect [24]. Gold nanoparticles (AuNPs) are used to load phytochemicals (curcumin, quercetin and paclitaxel), AuNPs (b-AuNPs). The combination of AuNPs-Cur, AuNPs-Tur, AuNPs-Qu and AuNPs-Pacli has good anti-tumor activity [25]. The nanomedicine method can make cyclosporine A and gefitinib co-deliver and enhance the therapeutic effect of drug-resistant lung cancer [26]. Biodegradable nanoparticles mediated erlotinib (ELTN) and Federatinib (FDTN) co-delivery to treat ELTN-resistant non-small cell lung cancer (NSCLC) by inhibiting the JAK2/STAT3 signaling pathway [27]. The drug micelles co-carrying paclitaxel and cisplatin exhibit superior anti-tumor activity than single drugs or their mixtures [28]. In ovarian cancer models, the co-delivery of wortmanning and cisplatin nanoparticles can synergically improve radiotherapy and chemotherapy and reverse platinum resistance [29]. Recent studies have shown that nano-carrier drug delivery systems have greatly improved the effectiveness of drugs in the treatment of cancer (Fig. 3).

As reported in previous studies, we provide a systematic overview of phytochemicals and phytochemicals in synergistic sensitization, reversal of drug resistance and reduction of toxic side effects from the perspective of their combined use in cancer therapy. And a detailed summary of the mechanism through which phytochemicals work. Concurrently, the delivery system is linked to nanomedicines to maximise the combined anti-tumour effect of synergistic phytochemicals and chemotherapeutic agents based on a nano-co-delivery system, and an overview of its nano-co-delivery system is presented. Finally, some opportunities and challenges in how to translate these insights into clinical benefits are discussed.

2. 2.Materials and methods

We searched English databases, including PubMed, Web of Science, and GeenMedical, then we screened relevant literature published in China and abroad. The databases were searched using the following terms: [“bioactivecompounds” OR“ Natural compound” OR“ natural product” OR“ traditional Chinese medicine” OR“ herb-medicine” AND“ cancer”]. Nanomedicine co-delivery is retrieved in the database using the following terms: [“nanomedicines ”AND“ cancer”]. According to the situation of different databases, the subject words are comprehensively searched in combination with keywords, topics, abstracts, and free words to ensure the systematization and integrity of literature retrieval (Fig. 1).

We searched all basic and clinical studies on the synergistic anti-tumor mechanism of natural compounds and traditional therapies and collected all confirmed targets. In order to ensure the authenticity and systematicness of the results, we included all cell and animal samples in relevant studies.

3. Rationale and advantages of combination therapy

Currently, the most common anticancer strategies include surgery, chemotherapy, radiotherapy, immunotherapy, molecularly targeted therapies, and so on. Among these approaches, chemotherapy is still one of the most effective methods. However, the conventional chemotherapeutic drugs show the limited efficacy for cancer treatment due to the tumor heterogeneity, the dose-limiting toxicity for cancer patients and the occurrence of drug-resistant. Therefore, the combined treatment of chemotherapeutic drugs and other therapeutic agents such as phytochemicals is an emerging strategy to augment the sensitization and/or overcome drug-resistance of cancer cells. Conventional monotherapy non-selectively targets the proliferating cells, eventually leading to indiscriminate attacks on all the cells, causing damage to both normal cells and cancer cells. The purpose of combination therapy is to combine the drugs of different mechanisms to produce synergistic effects or reduce side effects [30]. During the past years, various phytochemicals have emerged as potential chemosensitizing or reversing drug-resistance agents in cancer cells due to their low toxicity, multi-targeted properties as well as to $1 + 1 \geq 2$ effects. Increasing evidence has demonstrated that phytochemicals are low toxicity, safe, economical and valid multi-targeting drugs for the therapy of different malignant tumors and for enhancing the sensitization or reversing the resistance of chemotherapeutic drugs in cancer cells and significantly reducing the therapeutic dose and toxicity of single drugs. For example, in a phase I study, patients taking high doses of curcumin (8 g/ day) showed non-toxic, safe and tolerable effects [31]; in a clinical trial of the safety of oral ingestion of curcumin extract, no dose-limiting toxicity was observed after 16 weeks of treatment in patients with advanced colorectal cancer [32]. So the combination of chemotherapeutic drugs with phytochemicals in cancer treatment is attracting more and more attention.

3.1. Drug combination and TCM Compatibility: Different methods with the same results

Due to the complexity of human diseases including cancer, it is difficult to control cancer using the conventional “single compound, single target” approach. In addition, long-term repeated use of monotherapy by cancer patients can promote the resistance of cancer cells to the applied treatment [33]. Therefore, combined regimens referring to the co-delivery of two or more therapeutic drugs or a combination of different treatment methods is becoming a main trend in clinical treatment of cancer, increasing the proportion of patients who benefit have met with challenges of limited efficacy and significant toxicity [34]. Most importantly, increasing evidence shows that combination regimens for cancer therapy can generate synergistic anticancer effects, decrease the dosage of each compound, reduce the toxicity of single drugs, and suppress multi-drug resistance through different signaling pathways [35].

It’s worth mentioning that traditional Chinese medicine (TCM) is a unique medical system that helped ancient Chinese people treat diseases. For more than 2,500 years, TCM has advocated comprehensive treatment with prescription medicine [36]. Well known, multi-herb therapy called formulae is one of the most important characteristics of TCM. In agreement with drug combination, TCM formulae through combined plant species or minerals which follow specific compatibility rules to increase efficiency and reduce toxicity [35]. “Jun, Chen, Zuo and Shi” is widely used compatibility principle of designing a formula in TCM, in which one represents the main component, and others act as adjuvant ones to increase efficiency, reduce toxicity or promote the delivery of the main component [37].

Although the theory of drug combination and TCM compatibility is different, the purpose and result are the same. The combination of multiple drugs may simultaneously target diverse targets, subgroups or diseases. The drug design with distinct but related mechanisms can also play a role directly against a single disease such as cancer, thus generate more therapeutic benefits. Whether drug combination or TCM compatibility, the possible benefits include: 1) exert synergistic therapeutic efficacies, 2) reduce the dose but increase or maintain the same effect to prevent toxicity, 3) minimize or alleviate the development of drug resistance, 4) provide selective synergy (or efficacy synergy) against the target

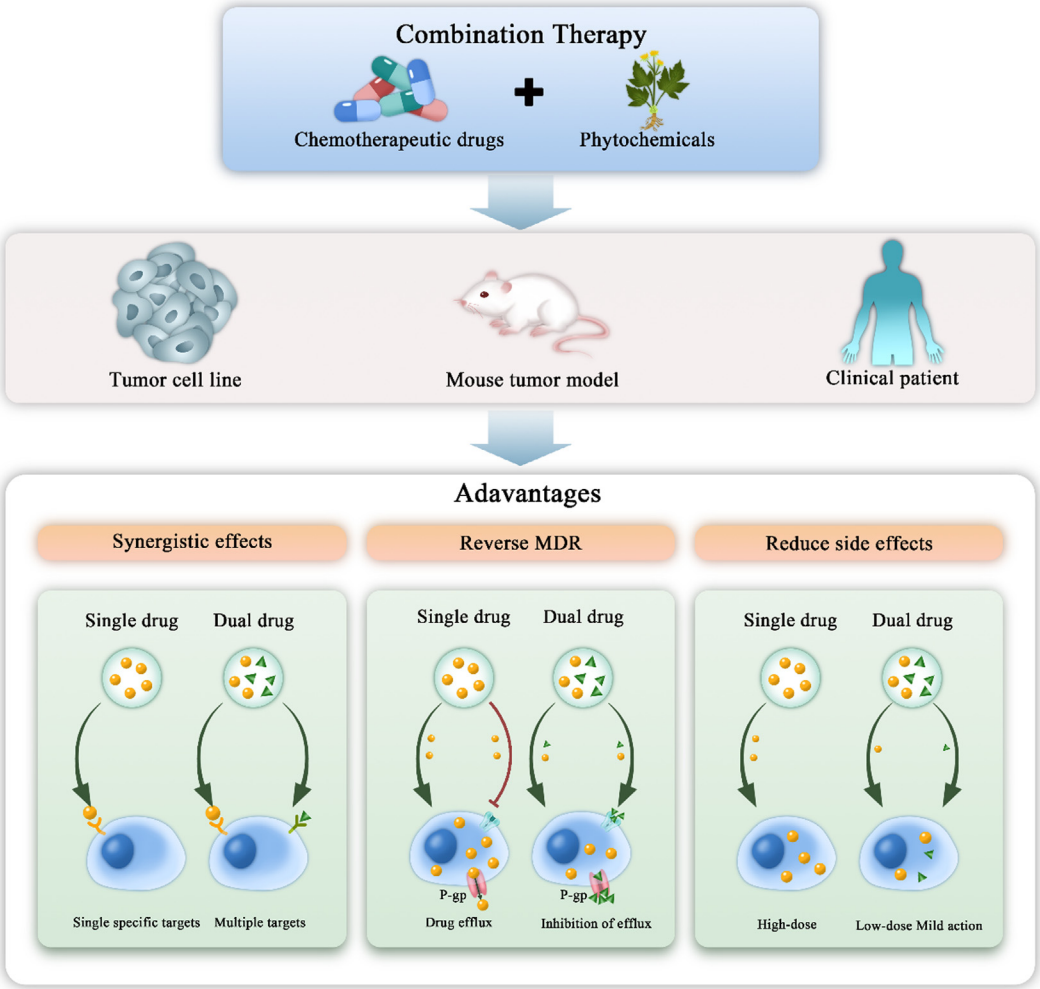

Fig. 4. Advantages of the combination of phytochemicals with standard chemotherapeutic drugs. The conventional chemotherapeutics used for the treatment and prevention of cancer are often associated with adverse side effects and development of chemoresistance. Phytochemicals acquired from botanicals possess immense anti-cancer potential. They are cost-effective, possesses minimal side effects, and are easily accessible. Chemotherapeutic drugs are mostly monotargeted and show toxicity in normal cells; however, in combination with different phytochemicals, they improve synergistic effects, reverse MDR, reduce side effects.

with the host (or toxicity antagonism). Because of these advantages, combination medication has been widely applied and has converted a major trend in the treatment of cancer and other human diseases. Although TCM formulae have confronted with many obstacles due to its inconceivable complexity. Previous studies have demonstrated that multiple components in multiple formulae can against multiple targets and exert synergistic function (Fig. 4).

3.2. Synergistic effects of phytochemicals in combination with chemotherapeutic agents and the overcoming of MDR resistance

Cancer remains one of the leading causes of death worldwide. Chemotherapy is a commonly used treatment approach for cancer treatment. However, the side effects and drug resistance are two major difficult problems for cancer treatment, which limits the effectiveness of these drugs. Therefore, it is urgent to find a harmless and effective anticancer drug for cancer treatment. The use of natural phytochemicals in combination therapy with conventional chemotherapeutics is an emerging strategy for the prevention and treatment of cancer, because these botanicals have various remarkable anti-cancer properties. Over the past few years, all kinds of multi-targeted phytochemicals have been investigated to enhance the efficacy of conventional chemotherapy. Current studies have elucidated that phytochemicals are able to strengthen the sensitivity of tumors to chemotherapeutic drugs [8]. Using one or several lower-toxic phytochemicals in combination with chemotherapy drugs can enhance the sensitivity of cancer cells to drugs and reduce the toxic and side effects of chemotherapy drugs, which is a strategy worthy of consideration (Table.1 and Fig. 5).

In addition, Chemotherapeutic resistance is also a major challenge for chemotherapeutic drug use. In recent years, a variety of multi-target phytochemicals have been shown to have the potential to reverse the resistance of cancer cells to chemotherapeutic drugs, in addition to the synergistic effects of their combination with chemotherapeutic drugs (Table 2 and Fig. 5).

Although phytochemicals have great potential in synergistic sensitization and reversal of chemotherapy resistance, most phytochemicals are only used in preclinical studies and need clinical trials to comprehensively evaluate their therapeutic value.

4. Approaches of combination therapy

Combination therapy, a treatment that combines two or more drugs, is a new strategy for cancer treatment [38]. The combination of phytochemicals and chemotherapeutic improves efficacy com-

Table 1
Synergistic effect of combination therapy between phytochemicals and chemotherapeutic drugs and mechanisms.

Cancer	Phytochemicals (plant name)	Chemotherapeutic Drugs	Targets	Ref
Lung cancer	Honokiol (*Magnolia officinalis*)	Paclitaxel	Synergistically induce apoptosis	[44]
		Bleomycin	Inhibit DNA polymerases Beta and Lambda	[45]
		Chloroquine	Induce cell death and inhibit autophagy	[46]
	Resveratrol (*Polygonum cuspidatum, mulberry, peanut, grape*)	Cisplatin	Enhance pro-apoptotic protein Bax and decrease anti-apoptotic protein Bcl-2 expression	[48]
		TRAIL	p53 independent and suppression of Akt/NF-kappaB signaling	[49]
	Gambogic acid (*Garcinia hanburyi tree*)	Cisplatin	Inactivate the mitogen-activated protein kinase (MAPK)/heme oxygenase 1 (HO-1) and NF-κB signaling pathways	[50]
		Adriamycin	Suppression of NF-KappaB signaling and P-glycoprotein function	[37]
		Gemcitabine	Synergistic effect	[51]
	Isochaihulactone (*South Bupleurum*)	Paclitaxel	Increase NSAID-activated gene-1 (NAG-1) expression	[52]
	Shikonin (*Zi Cao*)	Gefitinib	Inhibition of PKM2, cyclinD1 and STAT3	[54]
		Doxorubicin	Inhibit the expression of ATP-binding cassette transporter	[55]
Colorectal cancer	Honokiol (*Magnolia officinalis*)	Cisplatin	Synergistic effect	[76]
		Oxaliplatin	Inhibit COX-2,VEGF protein levels and phosphorylation of AKT,ERK1/2 and NF-κB P65	[77]
	Ursolic acid (*Fructus Mume*)	Oxaliplatin	Synergistic effect	[78]
			Induce apoptosis and reactive oxygen species production and inhibit the expression of drug-resistant genes	[79] -[80]
	β-elemene (*Curcuma wenyujin*)	Cetuximab	Inhibit epithelial-mesenchymal transition and induce ferroptosis	[81]
	Curcumin (*Curcumae Rhizoma*)	5-FU	Synergistic effect	[84]
		Oxaliplatin	Induce apoptosis and G2/M phase cell cycle arrest	[91]
		Oxaliplatin	Inhibit the NF-kappaB cell signaling pathway	[93]
	Bufalin (*Bufonis Venenum*)	5-FU	Reduce the anti-apoptotic proteins Bcl-2, Mcl-1 and XIAP, and enhance the pro-apoptotic proteins Bax and Bad	[85]
	Gossypol (*Cotton plant*)	5-FU	Silence TS and inhibit cyclin D1 and mTOR/p70S6K1 signaling pathways	[86]
	Tangeretin (*Citrus peel*)	5-FU	Accelerate the ROS/JNK mediated apoptotic pathway	[87]
	Gambogic acid (*Garcinia hanburyi tree*)	5-FU	Inhibit the expression of BIRC5,P53,TYMS	[88]
	Quercetin (*Rutin*)	5-FU	Synergistic effect	[89]
	Triptolide (*Tripterygium wilfordii*)	5-FU	Induce ROS production and inhibit NF- NF-kappaB activity	[90]
	Sulforaphane (*Cruciferous plants*)	Oxaliplatin	Synergistic effect	[92]
Hepatocellular carcinoma	Chrysin (*Oroxylum indicum, White pine mountain*)	Cisplatin	Increase the phosphorylation and accumulation of P53 through activation of ERK1/2	[118]
		Sorafenib	Modulat the phosphorylation of ERK1/2	[119]
	Chlorogenic acid (*honeysuckle*)	Regorafenib	Inhibit MAPK and PI3K/AKT/mTOR signaling pathways	[120]
		5-FU	Inhibit ERK activation by overproducing ROS	[121]
	Celastrol (*Celastrol*)	Lapatinib	Synergistic effect	[123]
		ABT-737	Up-regulate Noxa through oxidative stress	[124]
		Apatinib	Downregulating the expression of p-Akt and p-ERK, and upregulating the expression of Caspase-3 and Bax	[125]
	Capsaicin (*chili*)	Sorafenib	Increase caspase3, Bax in cells, inhibite Bcl-2 and induced autophagy	[126]
	Bufalin (*Bufonis Venenum*)	Sorafenib	Down-regulating ERK	[127]
	Silibinin (*Silybum marianum*)	Sorafenib	Inhibit STAT3/ERK/AKT phosphorylation	[128]
	Artesunate (*Artemisia annua*)	Sorafenib	Dual inhibition of RAF/MAPK and PI3K/AKT/mTOR pathways	[129]
Breast cancer	Thymoquinone (*black cumin*)	Paclitaxel	Synergistic effect	[142]
		Gemcitabine	Synergistic effect	[143]
		Doxorubicin	Synergistic effect	[144]
	Sulforaphane (*Cruciferous plants*)	Paclitaxel	Downregulating the NF-κB signaling pathway	[145]
		Adriamycin	Synergistic effect	[146]
		Docetaxel	Synergistic effect	[147]
		5-FU	Induce premature senescence and autophagic cell death	[148]
	Epigallocatechin gallate (*Green tea*)	Sunitinib	Inhibit IRS/MAPK signal transduction	[150]
	Quercetin (*Rutin*)	Lonidamine	Synergistic effect	[151]
	Resveratrol (*Polygonum cuspidatum, mulberry, peanut, grape*)	Doxorubicin	Inhibit autophagy	[152]
	Shikonin (*Zi Cao*)	Paclitaxel	Synergistic effect	[153]
	Honokiol (*Magnolia officinalis*)	Adriamycin	Downregulating mir-188-5p	[154]-[155]

(*continued on next page*)

Table 1 (*continued*)

Cancer	Phytochemicals (plant name)	Chemotherapeutic Drugs	Targets	Ref
Stomach cancer	Thymoquinone (*black cumin*)	Cisplatin	Inhibiting PI3K/AKT signaling pathway, activating the mitochondrial pathway, and down-regulating P-glycoprotein by up-regulating PTEN gene	[183]
		5-FU	Enhance the activation of both caspase-3 and caspase-9	[184]
	Licochalcone A (*licorice*)	5-FU	Up-regulating levels of Bax, cleaved-poly ADP ribose polymerase, tumor protein 53 and caspase 3	[185]
	Curcumin (*Curcumae Rhizoma*)	5-FU	Downregulating COX-2 protein and NF-kB signaling pathways	[186]
	Pterostilbene(*Blueberries, grapes*)	Sorafenib	Arresting cells in G1 phase and inducing autophagy and promoting apoptosis	[187188]
	Luteolin (*Resedaceae*)	Oxaliplatin	Through the Cyt c/caspase pathway	-[189]
	Hesperetin (*citrus*)	Cisplatin	Inhibit the phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K)/AKT signaling pathway and induce the mitochondrial pathway via upregulating PTEN expression	[190]
	Gambogic acid (*Garcinia hanburyi tree*)	5-FU	Regulate the metabolism	[192]
	Osthole (*Cnidium monnieri*)	Trastuzumab	Synergistic effect	[193]
	schisandrin B (*Schisandra chinensis*)	Apatinib	Synergistic effect	[194]
	Deguelin (*Derris trifoliata*)	Cisplatin	Synergistic effect	[195]
	β-asarone (*Rhizoma Acori Tatarinowii*)	Cisplatin	Inhibiting Tumor Glycolysis	[196]
	Crocin (*saffron*)	Cisplatin	Increased the expression of p53 and Bax, and significantly decreased the Bcl-2 expression	[197]
	Cucurbitacin E (*Cucumis melo L*)	Doxorubicin	inactivating AKT	[198]
Pancreatic cancer	Genistein (*Leguminous plants*)	5-FU	Induce apoptosis and autophagy	[212]
	6-Shogaol (*Zingiber officinale*)	Gemcitabine	Modulation of TLR4/NF-kappaB signaling	[213]
	Shikonin (*Zi Cao*)	Gemcitabine	Induce apoptosis and necroptosis	[214]
	Thymoquinone (*black cumin*)	Gemcitabine	Abrogation of notch1, PI3K/Akt/mTOR regulated signaling pathways	[215]
	Triptolide (*Tripterygium wilfordii*)	Cisplatin	Downregulate heat shock protein 27 (HSP27)	[216]
		Gemcitabine	Modulating BCL-2 and mitochondrial membrane potential	[219]
	Quercetin (*Rutin*)	Gemcitabine	Inhibition of the receptor for advanced glycation end products (RAGE) expression	[217]
	Resveratrol (*Polygonum cuspidatum, mulberry, peanut, grape*)	Doxorubicin	Downregulating P-glycoprotein	[218]
	Epigallocatechin gallate (*Green tea*)	Gemcitabine	Downregulating ERK phosphorylation	[220]
	Curcumin (*Curcumae Rhizoma*)	Celecoxib	Inhibition of COX-2	[221]
	Luteolin (*Resedaceae*)	Gemcitabine	Increasing cytochrome *c* expression and caspase activation	[222]
	Apigenin (*celery*)	Gemcitabine	Cycle arrest, down-regulation of the prosurvival factor p-Akt, and induction of apoptosis	[223]
Glioblastoma	Thymoquinone (*black cumin*)	Temozolomide	Synergistic effect	[232]
Urothelial carcinoma	Honokiol (*Magnolia officinalis*)	5-FU	Synergistic effect	[233]
Malignant glioma	Honokiol (*Magnolia officinalis*)	Temozolomide	Synergistic effect	[234]
Oral squamous cell carcinoma	Honokiol (*Magnolia officinalis*)	5-FU	Mitochondria mediated endogenous pathway	[235]
Hodgkin's lymphoma	Curcumin (*Curcumae Rhizoma*)	Doxorubicin	Synergistic effect	[236]
Retinoblastoma	Curcumin (*Curcumae Rhizoma*)	Carboplatin, Etoposide, Vincristine	Synergistic effect	[237]
Prostate cancer	Sulforaphane (*Cruciferous plants*)	Paclitaxel	Synergistic effect	[238]
		Docetaxel	Inducing apoptosis	[239]
Renal cancer	Resveratrol (*Polygonum cuspidatum, mulberry, peanut, grape*)	Paclitaxel	PI3K/Akt signaling pathway	[240]
Tract cancer	Epigallocatechin gallate (*Green tea*)	Cisplatin	Synergistic effect	[242]
Cervical cancer	Quercetin (*Rutin*)	Cisplatin	Inducing apoptosis	[243]

Table 1 (*continued*)

Cancer	Phytochemicals (plant name)	Chemotherapeutic Drugs	Targets	Ref
Bladder cancer	β-elemene (*Curcuma wenyujin*)	Cisplatin	Synergistic effect; ROS-AMPK signaling pathway	[244]-[245]
Ovarian cancer	β-elemene (*Curcuma wenyujin*)	Paclitaxel	Inhibite the growth, migration, invasion through STAT-NF-KB signaling pathway	[246]

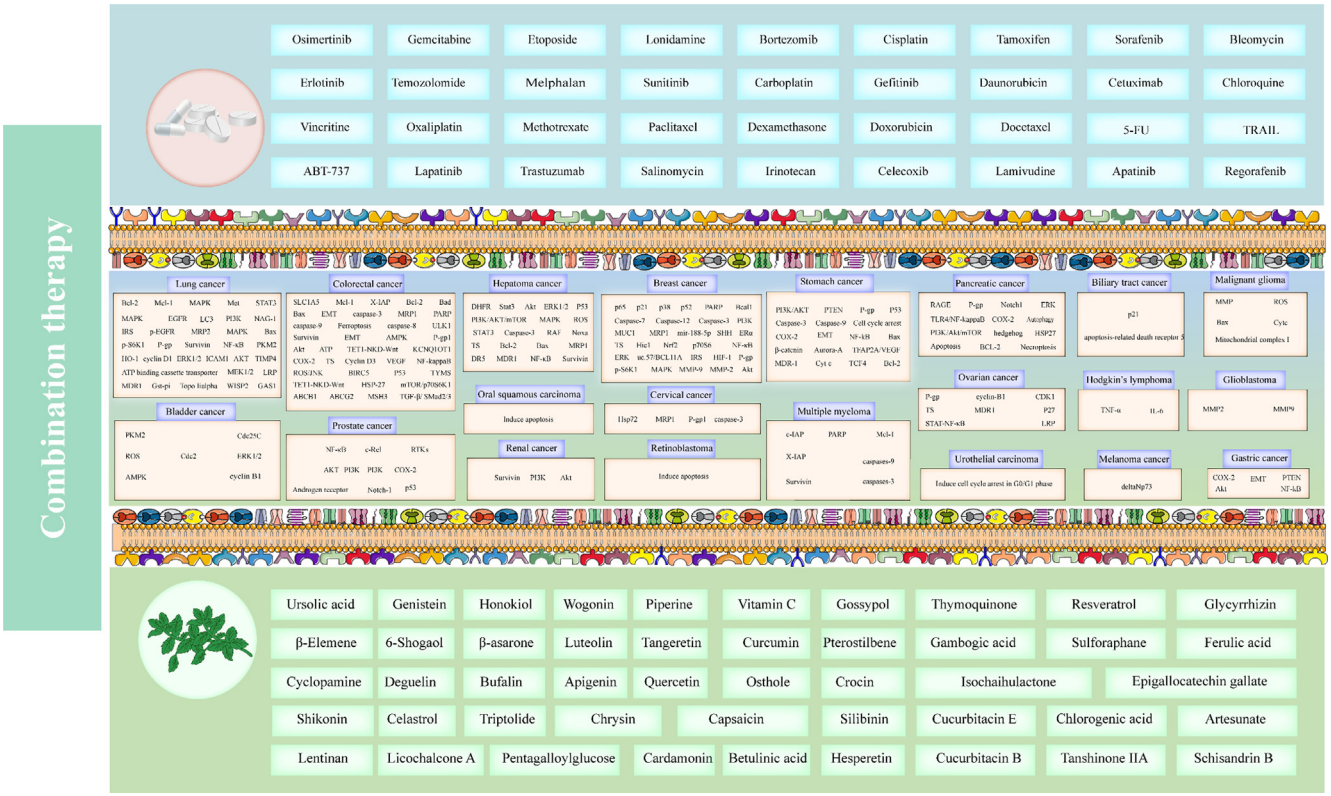

Fig. 5. Drugs and therapeutic targets of phytochemicals with chemotherapeutic drugs for reversing drug resistance and Synergistic effect.

pared to the mono-therapy, this is because drug combinations target key pathways in a synergistic or additive manner to achieve optimal effects. Currently available combination therapy approach can be divided into two classes of therapeutic approach: Simultaneous therapy and Sequential therapy. Here, we have reviewed reports of either Simultaneous therapy and Sequential therapy. In previous studies comparing mono-chemotherapeutic, combination therapy was associated with sufficient efficacy, inhibition of metastasis, inhibition of drug resistance and undesirable side effects (Fig. 6).

4.1. Simultaneous therapy

Since some natural compounds have chemosensitizing properties when combined with chemotherapeutic drugs. The schedule of administration of drugs can significantly affect the therapeutic outcome, either synergistic, antagonistic, or additive. The simultaneous Apigenin and 5-Fu treatment synergistically displayed apoptosis-inducing activities in HCT116 cells. Further studies have shown that apigenin can knock down forkhead box protein M (a transcription factor that regulates 5-FU sensitivity) and enhance apoptosis in HCT116 cells [39]. Shi-Yong Sun et al. explored that honokiol (HNK) can overcome Osim resistance. In nude mice, this combination also showed stronger growth inhibition against Osim-resistant xenograft tumors, including those with triple mutations of 19DEL, T790M, and C797S [40]. Co-delivery nanomedicines based on combination of phytochemicals with chemotherapeutic drugs also achieve simultaneous therapy. Meng-Dan Zhao et al. designed a "core-shell" polymeric nanoparticle-mediated curcumin and paclitaxel co-delivery platform. The results illustrated that the combination of curcumin and paclitaxel co-delivered by nanocellular carriers had synergistic anti-ovarian cancer effect on chemotherapy-sensitive human ovarian cancer cells (SKOV3) and multi-drug resistant mutant (SkOV3-TR30) in vitro, and also had excellent anti-tumor activity on ovarian tumor-bearing nude mice [41].

4.2. Sequential therapy

In addition to simultaneous therapy, Sequential therapy also plays a very important role. The sequential gambogic acid and adriamycin treatment synergistically displayed apoptosis-inducing

Table 2
MDR resistance overcome and reduce side effects by the combination of phytochemicals and mechanisms.

Cancer	Combination Effect	Phytochemicals (Plant name)	Chemotherapeutic Drugs	Targets	Ref
Lung cancer	Reversal of drug resistance	Curcumin (*Curcumae Rhizoma*)	Erlotinib	Downregulated the expressions of EGFR, p-EGFR, and survivin, and inhibited the NF-κB activation	[58]
			Gefitinib	Downregulated EGFR activity, suppressed receptor tyrosine kinases as well as ERK/MEK and AKT/S6K pathways	[59]
			Sulfinosine	Regulating the expression of MDR-related genes mdr1, gst-pi and topo lialpha	[60]
		Bufalin *(Bufonis Venenum)*	Gefitinib	Inhibiting Met/PI3K/Akt signaling pathway and inducing apoptosis	[61,62]
			Afatinib	Blocking of cMet/PI3K/AKT and cMet/MAPK/ERK pathways and inhibiting of epithelial-mesenchymal transition.	[63]
			Osimertinib	Degradation of MCL-1	[61]
		Gambogic acid *(Garcinia cambogia tree)*	Cisplatin	Inducing cell cycle arrest, apoptosis and down-regulating expression of LRP and MRP2 proteins	[64]
			Gefitinib	Reduced the phosphorylation level of AKT, MEK1/2 and ERK1/2 and increased expression ratio of Bax/Bcl-2	[65]
		Honokiol *(Magnolia officinalis)*	Osimertinib	Promoting the degradation of Mcl-1	[35]
		β-elemene *(Curcuma wenyujin)*	Cisplatin Erlotinib	Inhibiting the expression of P-gp	[66]
		Epigallocatechin-3-gallate *(Green tea)*	Cisplatin	Downregulated expression of GAS1, TIMP4, ICAM1 and WISP2	[67]
	Reduce side effects	Luteolin *(Resedaceae)*	Doxorubicin	Reverse DOX-mediated lung injury, resulting in reduced DOX chemotherapy toxicity	[68]
		Banxia Xiexin decoction	Irinotecan	Preventing and controlling the delayed diarrhea induced by Irinotecan in patients with non-small cell lung cancer and reducing its toxicity	[71]
		Shenqi Fuzheng injection	Platinum-based chemotherapy	Improve clinical efficacy and reduce toxic and side effects	[72]
Colorectal cancer	Reversal of drug resistance	Curcumin *(Curcumae Rhizoma)*	5-FU	Adjusting TET1-NKD-Wnt signal pathway to prevent the epithelial mesenchymal transition (EMT) progress	[95]
				Down-regulating P-GP and HSP-27	[97]
			Cisplatin	Down regulating the expression of KCNQ1OT1	[96]
			Oxaliplatin	Inhibiting EMT transformation by regulating TGF-β/ SMad2/3 signaling pathway	[98]
		Resveratrol *(Polygonum cuspidatum, mulberry, peanut, grape)*	Doxorubicin	Inhibiting the expression of P-gp1 and MRP1	[100]
		Quercetin *(Rutin)*	Doxorubicin	Inhibiting the expression of SLC1A5	[101]
		β-Elemene *(Curcuma wenyujin)*	5-FU	Inducing autophagy and cyclin D3 dependent cycle arrest	[102]
		Ursolic acid *(Fructus Mume)*	Oxaliplatin	Down-regulating ABCB1,ABCG2 and MSH3 genes to inhibit drug resistance	[81]
	Reduce side effects	Curcumin *(Curcumae Rhizoma)*	5-FU-based regimens	Significantly improve QoL and suppress systemic inflammation in patients with solid tumors who are under treatment with standard chemotherapy protocols.	[105]
		Honokiol *(Magnolia officinalis)*	5-FU	Synergistically stimulate cell apoptosis and enrich the non-toxic clinical effects of 5-FU in vivo and in vitro	[106]
		Arctigenin *(Forsythia viridissima)* Matairesinol *(Forsythia viridissima)*	Oxaliplatin	Protect against oxaliplatin induced neurotoxicity	[105]
		Astragaloside Ⅳ *(Astragalus)*	Oxaliplatin	Ameliorates oxaliplatin-induced neurotoxicity by modulating neuroinflammation and oxidative stress	[107]
		Huangqin formulas	Irinotecan	Improve irinotecan side effects	[109]
		PHY906			[110]
		Hange-Shashin-to			[111]
		Sairei-to			[112]
		Shengjiang Xiexin formulas			[113]
Hepatocellular carcinoma	Reversal of drug resistance	Bufalin *(Bufonis Venenu)*	Sorafenib	Inhibiting Akt signaling pathway	[131]
			5-FU	Down-regulating MRP1, reduced the expression of TS	
		Sulforaphane *(Cruciferous plants)*	TRAIL	Inducing ROS production to upregulate DR5 expression	[132]
		Pentagalloylglucose *(Anacardium occidentale L.)*	5-FU	Down-regulate MDR1 and LRP1	[133]
		Glycyrrhizin *(Licorice)*	Lamivudine Cisplatin	Inhibiting the cisplatin efflux from the cells	[134]
	Reduce side effects	Lentinan *(Lentinus edodes)*	Oxaliplatin	Inhibition of NF-κB, Stat3 and survivin signaling, attenuated the side effects produced by oxaliplatin induction	[135]
		PHY906 *(Scutellaria, licorice, peony and jujube)*	Sorafenib	Reduce toxic and side effects	[141–143]

Table 2 (*continued*)

Cancer	Combination Effect	Phytochemicals (Plant name)	Chemotherapeutic Drugs	Targets	Ref
Breast cancer	Reversal of drug resistance	Honokiol *(Magnolia officinalis)*	DOX	Inhibiting the expression of mucin 1 (MUC1) and multidrug resistance protein (MRP1)	[158]
		Quercetin *(Rutin)*	DOX	Downregulate P-glycoprotein expression to decrease DOX efflux as well as initiate mitochondria-dependent apoptotic pathways to accelerate DOX-induced apoptosis	[159]
				Downregulating the expression of hypoxia inducible factor-1(HIF-1)	[160]
		β-Elemene *(Curcuma wenyujin)*	Tamoxifen	Remolding the expression of estrogen receptor α(ERα)	[162]
		Gambogic acid *(Garcinia hanburyi tree)*	Paclitaxel	Down-regulating the SHH signaling pathway	[164]
		Shikonin *(Zi Cao)*	Tamoxifen	Downregulates BCL11A to inhibit PI3K/AKT and MAPK signaling pathways	[165]
		Ursolic acid *(Fructus Mume)*	Doxorubicin	Inhibiting P-gp function and destroying energy and related amino acid metabolism	[166]
	Reduce side effects	Tanshinone IIA *(Poria skin)*	Adriamycin	Reduced side effects including weight loss, bone marrow suppression, cardiotoxicity, and nephrotoxicity	[167]
		Quercetin *(Rutin)*	DOX	Reduce the toxicity of DOX	[160]
		Curcumin *(Curcumae Rhizoma)*	5-FU	Addition of curcumin during 5-FU treatment has been shown to protect normal cells from the toxic effects of 5-FU	[168]
Stomach cancer	Reversal of drug resistance	Resveratrol *(Polygonum cuspidatum, mulberry, peanut, grape)*	Doxorubicin	Inhibiting EMT through regulating PTEN/Akt signaling pathway	[200]
		Gossypol *(Cottonseed kernels)*	Gemcitabine	Shows synergism against gemcitabine resistance in GC cells with high BCL-2 expression	[201]
		Cardamonin *(Alpinia katsumadai)*	5-FU	Downregulated expression levels of P-glycoprotein, β-catenin and TCF4	[202]
		Epigallocatechin-3-gallate *(Green tea)*		Inactivation of TFAP2A/VEGF pathway and down-regulation of MDR-1 and P-gp expression	[203]
		Capsaicin *(chili)*	Cisplatin	Aurora-A protein degradation and apoptosis were increased	[204]
		Chrysin *(Oroxylum indicum(L.) Vent.)*	5-FU	Cell cycle arrest	[205]
		Bufalin *(Bufonis Venenu)*	Cisplatin	Through the AKT signaling pathway	[206]
	Reduce side effects	Triptolide *(Tripterygium wilfordii)*	Cisplatin	Exhibited excellent antitumor effect and no obvious side effects	[205]
		Wogonin *(Scutellaria)*	5-FU	Down-regulation of NF-kappaB	[208]
			Oxaliplatin	Reduction in oxaliplatin dose achieving the same response	[209]
		Vitamin C *(Jujube, Kiwi)*	Cisplatin	Effectively reduce the side effects caused by cisplatin	[210]
Pancreatic cancer	Reversal of drug resistance	Cyclopamine *(Veratrum)*	Gemcitabine	Inhibition of the hedgehog pathway	[225]
		Quercetin *(Rutin)*	Daunorubicin	Inhibiting the expression of P-glycoprotein (P-gp) expression	[226]
		Ursolic acid *(Fructus Mume)*	Gemcitabine	Inhibiting the expression of RAGE	[227]
	Reduce side effects	Betulinic acid *(White birch)*	Sorafenib	Inhibit proliferation and abolish clonogenic activity	[228]
Bladder cancer	Reversal of drug resistance	Curcumin *(Curcumae Rhizoma)*	Cisplatin	Through reactive oxygen species (ROS)-mediated activation of extracellular regulated kinase (ERK)1/2	[249]
		Shikonin *(Zi Cao)*		Significantly reduce the growth and metastasis of BC	[248]
Cervical cancer		Curcumin *(Curcumae Rhizoma)*	Cisplatin	Inhibiting the expression of P-gp1 and MRP1	[251]
Prostate cancer		Quercetin *(Rutin)*	Paclitaxel	Down regulating androgen receptor and inhibiting PI3K/Akt pathway	[252]
Melanoma		Quercetin *(Rutin)*	Temozolomide	Down regulate the expression of deltaNp73	[253]
Oral squamous cell Carcinoma	Reduce side effects	Honokiol *(Magnolia officinalis)*	5-FU	Did not increase the toxicity of 5-FU in vivo and in vitro	[237]
Prostate cancer		Curcumin *(Curcumae Rhizoma)*	Docetaxel	Reduced the therapeutic dose of docetaxel, and decreased the toxicity	[241]

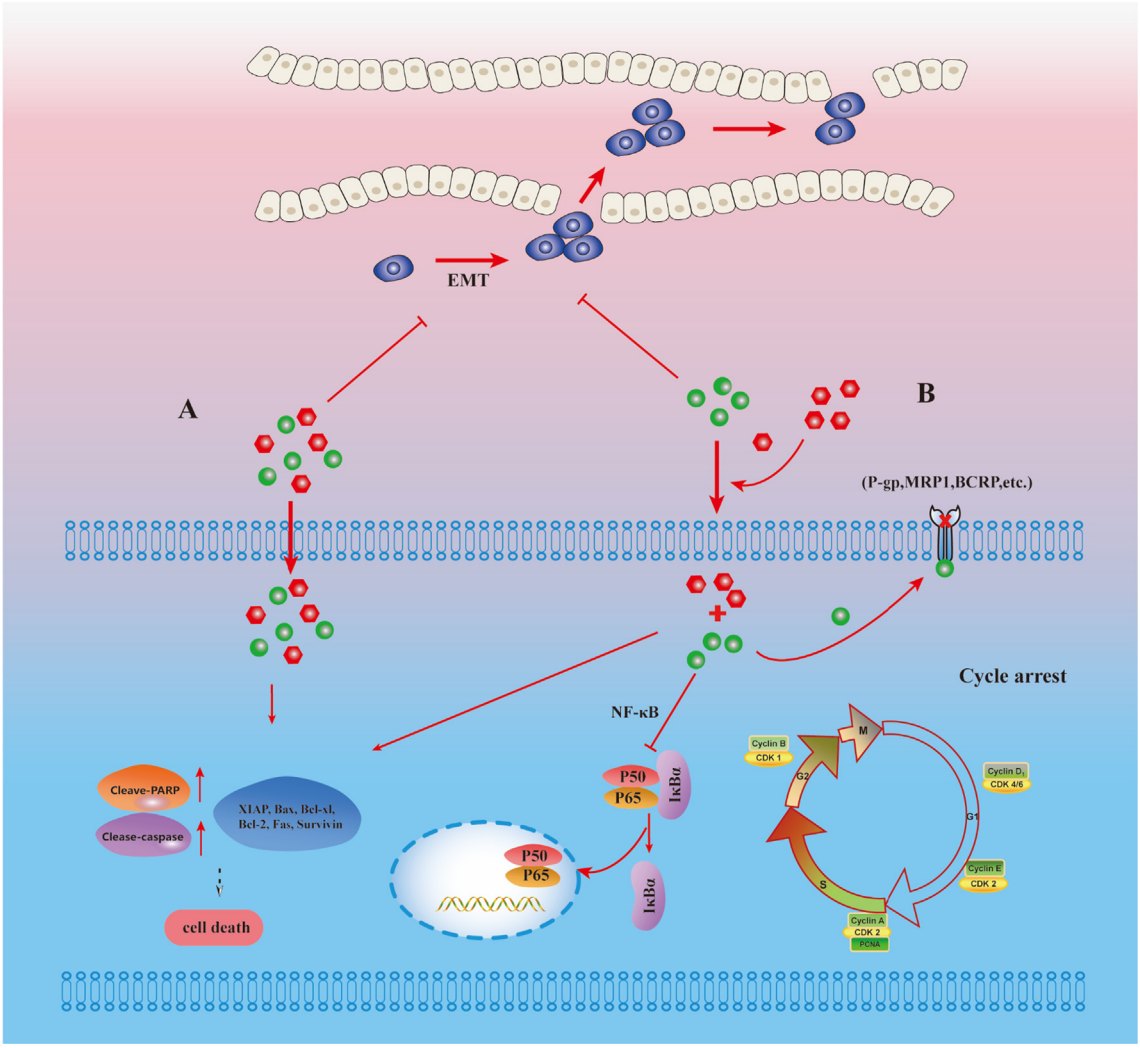

Fig. 6. Approaches of combination therapy induce: Simultaneous therapy and Sequential therapy. (A) Simultaneous therapy; (B) Sequential therapy.

activities in NSCLC cells, while simultaneous and reverse sequence treatments resulted in additive or antagonistic efficacy. Further study revealed that gambogic acid pretreatment could obviously inhibit NF-κB signaling pathways, which was related to adriamycin resistance [42]. Abdulmajeed A Bahman et al. investigated the combination regimens of natural phenolic compounds with sorafenib and demonstrated that resveratrol significantly strengthened the effect of sorafenib on Hep3b cells with administered in reverse order [43]. A battery of simultaneous and sequential experiments of fucoidan and cisplatin revealed that sequential treatments (either cisplatin → fucoidan or fucoidan → cisplatin) presented with great efficacy for inhibiting lung cancer cell viability, while the later sequential treatment showed higher efficacy [44]. Pretreatment with quercetin-loaded micelles followed by doxorubicin-loaded micelles efficiently retarded MDA-MB-231/MDR1 cell growth, and the probable mechanisms were the increasing intracellular doxorubicin accumulation and the downregulated P-glycoprotein expression after pretreated with quercetin-loaded micelles [45]. Moreover, sequential treatment can be achieved through varied release rate of the encapsulated drugs from nanocarriers. The quickly released curcumin from the temozolomide and curcumin co-loaded nanocarriers was supposed to sensitize the cancer cells to temozolomide, resulting in enhanced inhibitory effects on glioma cells [46].

5. Co-delivery nanomedicines for the combination of phytochemicals and chemotherapeutic drugs

Combined therapies can be challenging by many limitations, among which targeting to the precise cancerous tissue with minimal side effects are particularly challenging due to presence of highly organized physical, physiological and enzymatic barriers, leading to the limited drug partitioning and distribution to the target site and non-selective tissue toxicity. Moreover, a successful co-delivery of phytochemicals and chemotherapeutic drugs can be limited by the varying physiochemical and pharmacodynamic properties among different drug molecules, with extreme difficulty in optimizing the dosing and scheduling of drugs in combination therapy [47]. Due to their sub-micron size, nanocarriers can cross the physiological barriers and be taken up by the targeted cells, improving the bioavailability of therapeutic moieties. Thus, nanocarriers have been extensively studied for the delivery of anticancer drugs (Table 3).

At present, there are mainly liposomes, micelles, Polymeric nanoparticles and inorganic nanoparticles with co-delivery in tumor cells (Fig. 7). Liposomes are the most well studied and the most successful nanocarriers for clinical application to date, created from natural non-toxic phospholipids and cholesterol. Polymer micelles, composed of amphiphilic block copolymers with

Table 3
Co-delivery nanomedicines for the combination of phytochemicals and chemotherapeutic drugs.

Cancer	Phytochemicals (Plant name)	Chemotherapeutic Drugs	Nano formulation	Results	Ref
Lung cancer	Curcumin *(Curcumae Rhizoma)*	Cisplatin	Co-encapsulated Layer-by-layer nanoparticles	Co-encapsulated nanoparticles can reduce the degradation of CDD and CUR in the blood and increase the amount of drug accumulated in the tumor	[73]
		Adriamycin	Co-encapsulated PH-sensitive nanodrugs	U11-DOX/CUR NPs are a sustained-release, PH-responsive anti-tumor system, producing a strong synergistic effect	[74]
Colorectal cancer	Epigallocatechin-3-gallate *(Green tea)*	5-FU	Co-encapsulated nanoparticles made of gelatin and chitosan	Exhibited excellent anti-tumour activity, better bioavailability and longer in vivo circulation time	[114]
	Curcumin *(Curcumae Rhizoma)*	5-FU	Thiolate chitosan nanoparticles	Showed strong synergistic effects and bioavailability	[115]
			N,O-carboxymethyl chitosan nanoparticles		[116]
	Resveratrol *(Polygonum cuspidatum, mulberry, peanut, grape)*	Oxaliplatin	N, O-carboxymethyl chitosan nanoparticles	Combination of these two types of nanoparticles showed significantly greater anti-colon cancer activity than either the free drug or the nanoparticle alone	[117]
Hepatocellular carcinoma	Curcumin *(Curcumae Rhizoma)*	Doxorubicin	A glycyrrhetinic acid-modified chitosan-cystamine-poly (ε-caprolactone) copolymer micelle	Significantly facilitate the cell uptake of micelles	[137]
	Ursolic acid *(Fructus Mume)*	Sorafenib	pH-sensitive chitosan-conjugated mesoporous silica nanoparticle	Silica nanoparticles decorated with pH sensitive chitosan exhibited pH-responsive function and sustained release of ursolic acid and sorafenib	[140]
	Curcumin *(Curcumae Rhizoma)*	Sorafenib	pH-responsivelactosylatednanoparticles	LAC-SFN/CCM-NPs exhibited the highest tumor inhibition ability but low systemic toxicity	[141]
Breast cancer	Resveratrol *(Polygonum cuspidatum, mulberry, peanut, grape)*	Paclitaxel	Co-encapsulated PEGylated liposome	Effectively reverse the drug resistance of breast cancer cells to chemotherapy	[169]
	Quercetin *(Rutin)*		chondroitin sulfate (ChS)-coated mesoporous silica nanoparticles	Down-regulated the expression of P-gp and exhibited tumor-targeting ability, prolonged tumor retention time and effective anti-tumor effect without obvious toxicity to normal tissues in vivo.	[170,171]
	Curcumin *(Curcumae Rhizoma)*	Salinomycin	Co-encapsulated PLGA nanoparticles	Inducing G1 cell cycle arrest and limiting EMT	[172]
		Methotrexate	Co-encapsulated PLGA nanoparticles	Showed the synergic effect of MTX and CUR co-delivery on inhibiting the progression of breast cancer	[173]
	Epigallocatechin-3-gallate *(Green tea)*	Paclitaxel	Co-encapsulated PLGA nanoparticles	Sensitize breast cancer cells to paclitaxel	[174,175]
	Quercetin *(Rutin)*	Tamoxifen	Co-encapsulated PLGA nanoparticles	Demonstrate higher oral bioavailability, improved breast cancer efficacy and reduced hepatotoxicity	[176]
		Docetaxel	PLGA nanoparticles with hyaluronic acid -modification	Promoted cellular uptake and inhibited breast cell migration and invasion by initiating the Akt/MMP-9 signal pathway	[177]
	Resveratrol *(Polygonum cuspidatum, mulberry, peanut, grape)*	Doxorubicin	Co-encapsulated PLGA nanoparticles	Inhibited the doxorubicin -resistant breast tumor growth in tumor-bearing mice	[178]
	Curcumin *(Curcumae Rhizoma)*	Paclitaxel	PEGylated lipid bilayer coated mesoporous silica nanoparticle	Mesoporous silica nanoparticle could effectively accumulated in the tumor site and showed better anti-tumor effect	[179,180]
	Quercetin *(Rutin)*	Doxorubicin	Au nanocages	Exhibited fast release and strong cytotoxicity against MCF-7/ADR cells under NIR irradiation	[181]
	Piperine *(Piper nigrum L)*	Docetaxel	Multiwalled carbon nanotube	Exhibited better antitumor activity in MCF-7 and MDA-MB-231 breast cancer cells	[182]
	Quercetin *(Rutin)*	N-desmethyl tamoxifen	Multiwalled carbon nanotube	Reduced IC50 values and better cellular uptake in drug resistant MDA-MB-231 cells were observed.	[183]
Stomach cancer	Quercetin *(Rutin)*	Doxorubicin	Hyaluronic acid (HA)-modified silica nanoparticle	Decreased the expression of P-gp Wnt16, thus reshaping tumor microenvironment, reversing multidrug resistance and promoting doxorubicin activity	[211]
	Cucurbitacin B *(Cucumis sativus)*	Paclitaxel	ROS-responsive nanococktail (PCM) micelles	Reduce side effects and greatly increase the therapeutic efficacy of the drug	[212]
Pancreatic cancer	Betulinic acid *(Birch tree)*	Gemcitabine	Co-encapsulated PLGA-PEG polymer nanoparticles	Co-encapsulated PLGA-PEG polymer nanoparticles are more effective in inhibiting tumor growth in solid tumor models	[230]
	Curcumin *(Curcumae Rhizoma)*	Gemcitabine	Superparamagnetic iron oxide nanoparticle (SPION)	Efficiently delivered bioactive curcumin to pancreatic tumors while enhancing gemcitabine uptake and its efficacy	[231]

(*continued on next page*)

Table 3 (*continued*)

Cancer	Phytochemicals (Plant name)	Chemotherapeutic Drugs	Nano formulation	Results	Ref
	Ferulic acid *(Ferula assafoetida L.)*	Aspirin	Chitosan-coated solid lipid nanoparticles	Co-delivery significantly reduced the tumor volume in a mouse model of xenograft tumors	[232]
Glioblastoma	Quercetin *(Rutin)*	Temozolomide	DSPE-PEG2000 polymeric liposomes	Showed obvious accumulation of the liposomes in the brain, plasma concentrations of temozolomide and quercetin are significantly increased, and clearance is delayed in glioma rat model	[255]
Ovarian cancer	Curcumin *(Curcumae Rhizoma)*	Docetaxel	MPEG-PLA copolymer nanomicelles	Promoting tumor apoptosis, inhibiting tumor proliferation as well as suppressing tumor angiogenesis.	[256]
human renal cell carcinoma	Epigallocatechin-3-gallate *(Green tea)*	Sunitinib	Micellar nanocomplex	Significantly superior synergistical efficacy as well as tumor-targeted delivery facilitated by the carrier	[257]
Cervix cancer	Curcumin *(Curcumae Rhizoma)*	Doxorubicin	pH and redox dual-stage responsive mesoporous silica nanoparticles system	Prolong the time of the drug in the blood and improve the absorption of the drug by the cell.	[164]
Laryngeal cancer	Curcumin *(Curcumae Rhizoma)*	5-FU	Mesoporous silica nanoparticle	Produced a synergistic effect on tumor growth	[259]
Cervical cancer	Resveratrol *(Polygonum cuspidatum, mulberry, peanut, grape)*	Doxorubicin	Gold nanoparticles (AuNPs)	The Dox-GNPs complexes showed a strong accumulation inside the cancer cells	[260]
prostate cancer	Epigallocatechin-3-gallate *(Green tea)*	Gelatin-doxorubicin	Gold nanoparticles (AuNPs)	Effective accumulation in PC-3 cells by receptor-mediated endocytosis and significantly inhibit of the prostate cancer cells proliferation	[261]

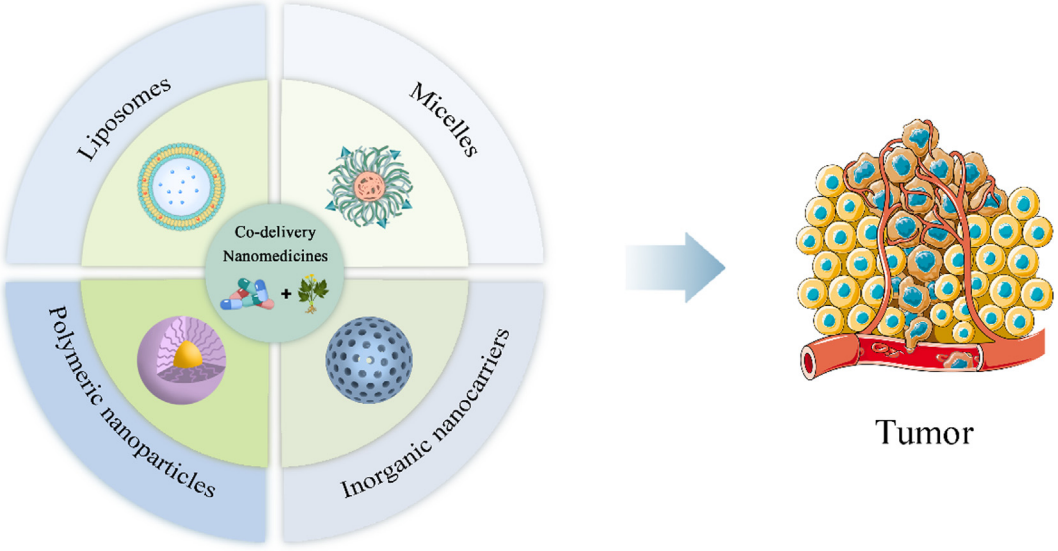

Fig. 7. Co-delivery nanomedicines based on combination of phytochemicals with chemotherapeutic drugs therapeutics. Examples of co-delivery nanomedicines based on combination of phytochemicals with chemotherapeutic drugs.

hydrophilic shells and hydrophobic cores, are a promising drug delivery system for hydrophobic drugs. Micelles possess many distinct features among various nanocarriers, such as co-encapsulation ability of different drugs, small size, easy surface-functionalization, good biodegradability, and biocompatibility for intravenous injection, making them good candidates for drug co-delivery. Mixed micelles will promote passive targeted drug delivery by enhancing permeability and retention (EPR) effects and active targeted drug delivery by binding polymers with ligands or antibodies to specific receptors or antigens on the surface of tumor cells. Poly (DL-lactide-co-glycolic acid) (PLGA) are a family of FDA-approved biodegradable polymers, which is one of the most used biodegradable polymers for development of nanomedicines due to its biocompatibility, sustainable release properties, low toxicity controlled. It can encapsulate both hydrophilic and hydrophobic drugs. Lastly, for inorganic nanomaterials, Mesoporous silica nanoparticles have been proposed as suitable inorganic drug carriers because of their large surface area and adjustable pore diame-

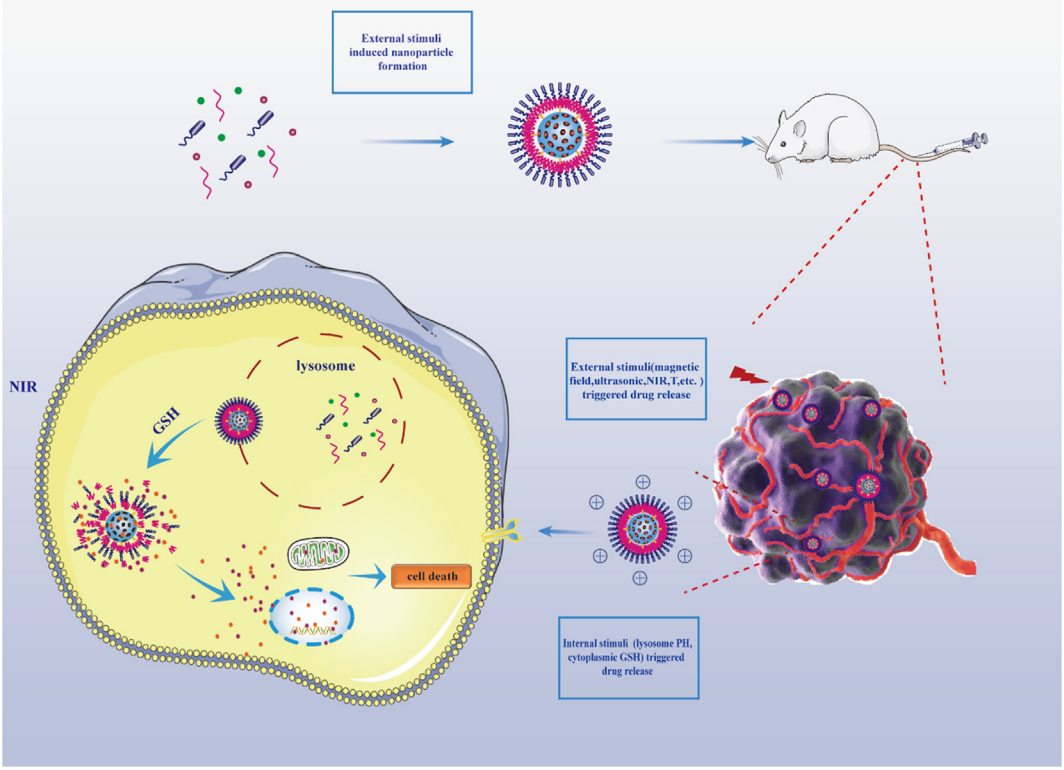

Fig. 8. Internal stimuli and external stimuli responsive polymeric nanoparticles as emerging controlled drug release systems.

ter, relatively uniform size, pore volume, low cytotoxicity, high biocompatibility, and their easily modified internal and external surface.

Due to improved permeability and retention (EPR) effects and impaired lymphatic drainage in tumor tissues, nanocarriers are considered to be a promising drug carrier for tumor. As mentioned before, decoration of the nanocarriers with ligands for active targeting can further facilitate the uptake of the drugs into the cells. The nanocarriers are released in cells can be divided into two categories. Among them, tumor internal microenvironment stimuli-responsive drug delivery systems have been widely concerned in tumor therapy (Fig. 8), which could increase the specificity of drug delivery. Another the external stimuli (Fig. 8), such as thermal, could also affect the fate of nanocarriers inside the biological systems.

6. Lung cancer

6.1. Combination of chemotherapeutics and phytochemicals

6.1.1. Synergistic effect of combination therapy

Honokiol is important active ingredient of traditional Chinese medicine Magnolia officinalis, which has multiple pharmacological effects, including antibacterial, antioxidant, antithrombotic, anti-cancer, anti-inflammatory, liver protection, and so on [48]. In lung cancer, honokiol combined with paclitaxel synergistically kill H1650 (paclitaxel-sensitive), H1299, and H1650/PTX cells (intrinsic and acquired paclitaxel-resistant, respectively) by inducing paraptosis [49]. Honokiol also inhibits DNA polymerases Beta and Lambda and increases Bleomycin sensitivity of A549 cells [50]. In addition, it also acts synergistically with chloroquine to induce cell death in NSCLC and inhibit autophagy [51].

Resveratrol mainly comes from Polygonum cuspidatum, mulberry, peanut, grape and other plants. It is a polyphenol compound. Previous experimental studies have shown that resveratrol has an anti-cancer effect on lung cancer [52]. Resveratrol in combination with cisplatin displayed a strong synergistic effect to promote cell death by enhancing Bax and decreasing Bcl-2 expression [53]. It can also further sensitize lung cancer cells to TRAIL by p53 independent and suppression of Akt/NF-kappaB signaling [54].

Gambogic acid (GA) is a dry resin secreted by the Garcinia cambogia tree. It is a natural compound with a polyprenylated xanthone structure and has significant anti-tumor pharmacological activity against a wide range of cancer cells. In lung cancer, GA sensitized NSCLC to cisplatin treatment in vitro and in vivo by inactivating the mitogen-activated protein kinase (MAPK)/heme oxygenase 1 (HO-1) and NF-κB signaling pathways [55]. In addition, gambogic acid inhibition of NF-KappaB signaling pathway and p-glycoprotein function synergistically enhanced adriamycin-induced apoptosis of lung cancer cells [42]. It also has a synergistic effect in combination with gemcitabine in lung cancer [56].

Isochaihulactone (K8) is a natural compound extracted from the Chinese traditional herb South Bupleurum. K8 was demonstrated to enhance paclitaxel-induced death in human lung cancer cells, and its enhancement was associated with increased expression of NSAID-activated gene-1 (NAG-1). Thus, paclitaxel combined with K8 has synergistic anti-tumour activity against lung cancer cells [57].

Shikonin (SHK) is the main biologically active ingredient extracted from shikonin root, also known as "Zi Cao" in traditional Chinese medicine. Recent research have elucidated that SHK can be a potential novel drug for the treatment of wound healing, cancer and inflammation [58]. In lung cancer, gefitinib targets mutant EGFR non-small cell lung cancer, but it is less effective in treating wild-type EGFR tumour. SHK was demonstrated to not only inhibit the growth of wild-type EGFR lung cancer cells, but also enhance anti-tumor effect of gefitinib in wild-type EGFR lung cancer cells in vitro and in vivo by the inhibition of PKM2, cyclinD1 and STAT3

[59]. In addition, SHK enhances the anti-tumor effect of doxorubicin by inhibiting the expression of ATP-binding cassette transporter in lung cancer cells [60]. EGCG may act synergistically with sunitinib in lung cancer and breast cancer because it can inhibit IRS/MAPK signal transduction induced by sunitinib [61].

6.1.2. MDR resistance overcome by the combination of phytochemicals

Curcumin, an effective component from traditional Chinese medicine Curcumae Rhizoma, exhibits a broad spectrum of anticancer effect and can apply to a variety of cancer types including respiratory system, digestive system, blood system, urinary system, reproductive system, and so on [62]. Recent studies in vivo and in vitro have shown that curcumin can reverse the resistance of lung cancer to chemotherapy drugs. Curcumin significantly increased the efficacy of erlotinib against erlotinib-resistant NSCLC cells, and therefore, curcumin may be a potential adjuvant therapy for NSCLC patients during erlotinib treatment [63]. The combination of curcumin and gefitinib synergistically inhibited Sp1 and blocked the interaction between Sp1 and HADC1, in addition to significantly downregulating EGFR activity, receptor tyrosine kinase and ERK/MEK and AKT/S6K pathways in drug-resistant NSCLC cells [64]. Moreover, curcumin and sulfinosine overcome MDR in non-small cell lung carcinoma cell line (NSCLC) by regulating the expression of MDR-related genes mdr1, gst-pi and topo Iialpha [65].

Bufalin is the main anti-tumor active ingredient of traditional Chinese medicine *Bufonis Venenum* in China. Recent studies have shown that bufalin has the potential to reverse the drug resistance. In lung cancer, bufalin reversed the drug resistance of lung cancer cells to gefitinib by inhibiting Met/PI3K/Akt signaling pathway and inducing apoptosis [66,67]. Bufalin reverses resistance to afatinib by modulating hepatocyte growth factor in H1975 lung cancer cells [68]. Bufalin enhances the therapeutic effect of osimertinib in patients with osimertinib-resistant EGFR mutant lung cancer by degrading MCL-1 [66].

Gambogic acid (GA) combined with cisplatin also produced marked anti-growth activity by inducing cell cycle arrest, apoptosis and down-regulating expression of LRP and MRP2 proteins in lung cancer cells [69]. The combined treatment GA and gefitinib significantly enhanced the anti-tumor effect of gefitinib on EGFR-T790M mutant NCI-H1975 cells, indicating that GA had the possibility of overcoming the drug resistance obtained by EGFR activating mutation [70].

In addition to the above-mentioned phytochemical drugs, some other drugs derived from traditional Chinese medicine have also been confirmed to have the effect of reversing tumor resistance. Honokiol could reverse the resistance of EGFR-mutant non-small cell lung cancer (NSCLC) to osimertinib by promoting the degradation of Mcl-1 [40]. β-elemene could reverse the resistance of cisplatin and erlotinib by inhibiting the expression of P-gp [71]. In lung cancer, DNA methylation can lead to gene silencing at the transcriptional level, which is related to the acquisition of the resistance to chemotherapy drugs. EGCG could re-sensitize non-small cell lung cancer cells to cisplatin through demethylation of target genes related to cell death [72].

6.1.3. Side-effects suppression by the combination of phytochemicals

Doxorubicin (DOX) treatment alone diminishes antioxidant capacity and anti-inflammatory cytokines in the lung and enhances oxidative stress leading to reduced survival [73]. Luteolin (LUT) is found in vegetables and fruits and have anti-inflammatory, anti-oxidant and apoptosis-inducing pharmacological effects [73]. In vivo experiments have demonstrated that DOX combined with LUT can reverse DOX-mediated lung injury, resulting in reduced DOX chemotherapy toxicity.

Irinotecan is a clinically proven first-line chemotherapy agent for the treatment of colorectal cancer, lung cancer, pancreatic cancer and other cancers [74]. However, the diarrhea associated with clinical use of irinotecan is debilitating and, in severe cases, life-threatening. Banxia Xiexin decoction is an effective herbal formula for the treatment of gastroenteritis, ulcerative colitis, vomiting and diarrhea, and is composed of seven herbs [75]. A clinical trial demonstrated that the combination of Banxia Xiexin decoction and Irinotecan was effective in preventing and controlling the delayed diarrhea induced by Irinotecan in patients with non-small cell lung cancer and reducing its toxicity [76]. Another study had shown that Shenqi Fuzheng injection (Shenqi Fuzheng injection) combined with platinum-based chemotherapy for the treatment of advanced NSCLC could improve clinical efficacy and reduce toxic and side effects [77].

6.2. Co-delivery nanomedicines for combination of chemotherapeutics and phytochemicals

Layer-by-layer nanoparticles co-encapsulated with cisplatin (CDDP) precursor drug and curcumin (CUR) have better cytostatic efficiency than free CDDP/CUR. Co-encapsulated nanoparticles can reduce the degradation of CDD and CUR in the blood and increase the amount of drug accumulated in the tumour, which can improve the synergistic response and maximise the therapeutic effect in lung cancer, thus overcoming drug resistance and reducing adverse effects [78]. Yuan Hong et al. designed PH-sensitive nanodrugs (U11-DOX/CUR NPs) co-encapsulated with curcumin and adriamycin. In vitro and in vivo experiments demonstrated that U11-DOX/CUR NPs are a sustained-release, PH-responsive anti-tumour system, producing a strong synergistic effect [79]. Moreover, Zhen Liang et al. designed a multi-nanometer platform for the co-delivery of cisplatin prodrugs, vinorelbine and all-trans retinoic acid, which can synergistically inhibit the development of lung cancer in vitro and in vivo [80].

7. Colorectal cancer

7.1. Combination of chemotherapeutics and phytochemicals

7.1.1. Synergistic effect of combination therapy

Honokiol exert a wide range of anticancer activities in colorectal cancer in vitro and in vivo by modulating multiple signaling pathways and acting synergistically in combination with chemotherapeutic agents [81]. The combined treatment of honokiol and cisplatin could synergistically inhibit the proliferation of CT26 cells [82]. Honokiol combined with oxaliplatin enhanced anti-cancer effects in HT29 cells by inhibiting COX-2,VEGF protein levels and phosphorylation of AKT,ERK1/2 and NF-κB P65 [83].

Ursolic acid (UA), a natural pentacyclic triterpenoid, is extracted from traditional Chinese medicinal herbs, such as *Fructus Mume*, *Fructus Ligustri Lucidi*, *Gardeniae Fructus*, *Hedyotis diffusa Willd*, etc. In colorectal cancer, the combination of UA and oxaliplatin can increased anti-tumor effect in RKO cells [84]. In colorectal cancer, UA synergistically strengthened the therapeutic effects of oxaliplatin [85], UA enhanced the therapeutic effect of oxaliplatin on colorectal cancer by inducing apoptosis and reactive oxygen species production and inhibiting the expression of drug-resistant genes [86].

In addition to the phytochemicals mentioned above, a number of other medicines derived from traditional Chinese medicine have been shown to have synergistic effects. In colorectal cancer, β-elemene can increase the sensitivity of KRAS mutant colorectal cancer patients to cetuximab treatment by inhibiting epithelial-mesenchymal transition and inducing ferroptosis, providing KARs

mutant colorectal cancer patients with new treatment strategy [87]. Both 5-FU and oxaliplatin are important chemotherapeutic agents in the treatment of colorectal cancer [88,89], and a variety of phytochemicals have been found to have synergistic effects with both 5-FU and oxaliplatin. In vitro and in vivo experiments have demonstrated the synergistic effect of curcumin, bufalin, gossypol, tangeretin, gambogic acid, quercetin, triptolide and other phytochemicals in combination with 5-FU. Curcumin combined with 5-FU improved the sensitivity of 5-FU to colorectal cancer cells [90], indicating that curcumin combined with 5-FU had a synergistic sensitization effect. Bufalin combined with 5-FU induces higher levels of apoptosis in colorectal cancer cells by reducing the anti-apoptotic proteins Bcl-2, Mcl-1 and XIAP, and enhancing the pro-apoptotic proteins Bax and Bad [91]. Gossypol enhances the anti-tumour effect of 5-FU by silencing TS and inhibiting cyclin D1 and mTOR/p70S6K1 signaling pathways [92]. The combination of tangeretin and 5-fluorouracil produces synergistic effects by regulating the ROS/JNK pathway [93]. Gambogic acid enhances the chemosensitivity of colorectal cancer cells to 5-fluorouracil by inhibiting the expression of BIRC5,P53,TYMS [94]. Quercetin enhances the therapeutic effect of 5-fluorouracil on colorectal cancer cells by regulating p53 [95]. Triptolide enhanced the sensitivity of colorectal cancer to 5-FU by inducing ROS production and inhibiting NF- NF-kappaB activity [96]. Meanwhile, previous trials have shown that curcumin and sulforaphane synergistically enhance the efficacy of oxaliplatin. Curcumin in combination with oxaliplatin acts synergistically by inducing apoptosis and G2/M phase cell cycle arrest [97]. Sulforaphane and oxaliplatin alone had a dose-dependent inhibitory effect on the growth of Caco-2 cells, and when the two were used in combination, enhanced the inhibitory effect on the cells [98]. In addition, curcumin enhances the antitumor and antimetastatic effects of capecitabine in colorectal cancer by inhibiting the NF-kappaB cell signaling pathway [99].

7.1.2. MDR resistance overcome by the combination of phytochemicals

Curcumin can not only synergistically enhance the effect of 5-FU and oxaliplatin, but also reverse the resistance of 5-FU and oxaliplatin to colorectal cancer. Curcumin could reverse 5-fluorouracil resistance by adjusting TET1-NKD-Wnt signal pathway to prevent the epithelial mesenchymal transition (EMT) progress [100], and also reverse the resistance of colorectal cancer to cisplatin by down regulating the expression of KCNQ1OT1 [101]. P-gp and HSP-27 are related genes of multidrug resistance. Curcumin can enhance the efficacy of 5-FU on HCT8/5-FU by down-regulating P-GP and HSP-27 [102]. Moreover, Curcumin regulates oxaliplatin resistance in CRC by inhibiting EMT transformation by regulating TGF-β/ Smad2/3 signaling pathway [103], and curcumin has also been shown in vivo to ameliorate resistance to oxaliplatin [104].

In addition to curcumin, resveratrol, quercetin, elemene and ursolic acid can reverse chemotherapy resistance in colorectal cancer. Resveratrol could reverse multidrug resistance by inhibiting the expression of P-gp1 and MRP1 [105]. Quercetin also overcomed doxorubicin resistance by inhibiting the expression of SLC1A5 [106]. β-Elemene not only has synergistic sensitization effect, but also plays a unique role in reversing drug resistance. In colorectal cancer, β-elemene reversed the resistance of 5-FU due to p53 deficient colorectal cancer cells by inducing autophagy and cyclin D3 dependent cycle arrest [107]. Ursolic acid can enhance the therapeutic effect of oxaliplatin on colorectal cancer by down-regulating ABCB1,ABCG2 and MSH3 genes to inhibit drug resistance [86].

7.1.3. Side-effects suppression by the combination of phytochemicals

First-line chemotherapy drugs for colorectal cancer include 5-FU, oxaliplatin, irinotecan, etc., but they can cause obvious side effects, such as cardiotoxicity of 5-FU [108], neurotoxicity of oxaliplatin [109], and diarrhea of irinotecan [74].

In a phase II double-blind randomized study, curcumin-based drugs combined with chemotherapy showed higher efficacy in reducing adverse by-effect and enhancing quality of life in patients with solid tumors such as colorectal cancer [110]. The combination of honokiol and 5-fluorouracil (5-FU) can synergistically stimulate cell apoptosis and enrich the non-toxic clinical effects of 5-FU in vivo and in vitro [111]. The dried fruit of *Forsythia viridissima* have been developed in traditional medicine for moderate fever, pain, vomiting and nausea. Experimental studies have shown that the main components arctigenin and matairesinol can protect against oxaliplatin induced neurotoxicity [112]. In addition, astragaloside Ⅳ ameliorates oxaliplatin-induced neurotoxicity by modulating neuroinflammation and oxidative stress [113]. For irinotecan induced diarrhea, the experiment proved that Huangqin formulas [114], PHY906 [115], Hange-Shashin-to [116], Sairei-to [117], Shengjiang Xiexin formulas [118], can improve the side effects of irinotecan.

7.2. Co-delivery nanomedicines for combination of chemotherapeutics and phytochemicals

Ruoning Wang et al. developed a novel oral delivery system in which EGCG and the first-line chemotherapeutic agent 5-FU were co-encapsulated in nanoparticles made of gelatin and chitosan, which exhibited excellent anti-tumour activity, better bioavailability and longer in vivo circulation time [119]. Curcumin and 5-FU-loaded thiolate chitosan nanoparticles also showed strong synergistic effects and bioavailability [120]. In addition, Curcumin and 5-FU-loaded N,O-carboxymethyl chitosan nanoparticles have the same therapeutic effect in colorectal cancer [121].

For the first-line chemotherapy drug oxaliplatin, Wang Yaowen et al. prepared N, O-carboxymethyl chitosan nanoparticles loaded with oxaliplatin and resveratrol by ionic crosslinking and emulsifier crosslinking. The combination of these two types of nanoparticles showed significantly greater anti-colon cancer activity than either the free drug or the nanoparticle alone, and the same therapeutic effect was demonstrated in vivo [122].

8. Hepatocellular carcinoma

8.1. Combination of chemotherapeutics and phytochemicals

8.1.1. Synergistic effect of combination therapy

Chrysin is a naturally occurring flavonoid found in many plants, honey and propolis and has a number of pharmacological activities such as anti-cancer, pro-apoptotic, anti-angiogenic, anti-metastatic, immunomodulatory and antioxidant properties [123]. Study demonstrates synergistic enhancement of cisplatin and sorafenib in hepatocellular carcinoma by chrysin. The combination of chrysin and cisplatin increased the phosphorylation and accumulation of P53 through activation of ERK1/2 in Hep G2 cells, leading to upregulation of the apoptotic proteins Bax and DR5 and inhibition of Bcl-2, thus exerting a synergistic effect [124]. Similarly, chrysin enhances the therapeutic effect of sorafenib by modulating the phosphorylation of ERK1/2 [125].

Chlorogenic acid is a natural polyphenol with antioxidant, antibacterial, anti-inflammatory and other pharmacological effects. Chlorogenic acid in combination with Regorafenib enhances the therapeutic effect on hepatocellular carcinoma by inhibiting MAPK and PI3K/AKT/mTOR signaling pathways [126]. In addition, Chlorogenic acid Chlorogenic acid inhibits ERK activation by overproducing ROS, thus making 5-FU sensitive to hepatocellular carcinoma [127].

Celastrol (Cel) is a quinone-methylated triterpenoid extracted from Tripterygium wilfordii [128]. Celastrol enhanced the apoptotic effect of lapatinib on hepatoma cells [129]. Celastrol combined with ABT-737 up-regulated Noxa through oxidative stress and played a synergistic anticancer role [130]. Moreover, the use of Apatinib in combination with Celastrol produced a synergistic effect by inhibiting the expression of p-Akt and p-ERK and increasing the activation of Caspase-3 and Bax, significantly inhibiting the ability of Hep3B cells to proliferate, migrate and invade [131].

Sorafenib is a first-line drug for advanced liver cancer. In addition to the synergistic effects of the phytochemicals and chemotherapeutic drugs mentioned above on hepatocellular carcinoma, there are also many traditional Chinese monomers that can have synergistic therapeutic effects with sorafenib, the first-line drug in the treatment of liver cancer [132]. The combination of capsaicin and sorafenib increased caspase3, Bax in cells, inhibited Bcl-2 and induced autophagy, thus playing a synergistic role [132]. Bufalin enhanced the antiproliferative effect of sorafenib in hepatocellular carcinoma by down-regulating ERK [133]. Combination therapy with sorafenib and silibinin synergistically targets HCC cells and tumor stem cells by inhibiting STAT3/ERK/AKT phosphorylation [134]. In addition, Sorafenib combined with artesunate promoted the dual inhibition of RAF/MAPK and PI3K/AKT/mTOR pathways and promoted cell death [135].

8.1.2. MDR resistance overcome by the combination of phytochemicals

Bufalin also has the effect of reversing drug resistance in hepatocellular carcinoma. In hepatocellular carcinoma (HCC), bufalin could overcome the drug resistance of HCC to sorafenib by inhibiting Akt signaling pathway [136]. In addition, Bufalin inhibited the activity of drug efflux pump by down-regulating MRP1, reduced the expression of TS in BEL-7402/5-FU cells, and enhanced the sensitivity of drug-resistant HCC cells to 5-FU [136].

In addition to bufalin, sulforaphane, Pentagalloylglucose and glycyrrhizin have the effect of reversing drug resistance against chemotherapy in hepatocellular carcinoma cells. In hepatocellular carcinoma (HCC), Sulforaphane enhances TRAIL sensitivity in TRAIL-resistant hepatocellular carcinoma by inducing ROS production to upregulate DR5 expression [137]. Pentagalloylglucose combined with 5-FU can significantly down-regulate MDR1 and LRP1, which may reverse 5-FU resistance [138]. The combination of glycyrrhizin and lamivudine can inhibit cisplatin excretion from cells, thus enhancing the therapeutic effect of cisplatin on hepatocellular carcinoma [139].

8.1.3. Side-effects suppression by the combination of phytochemicals

The main drug treatments for hepatocellular carcinoma are chemotherapeutic agents such as platinum, adriamycin and paclitaxel, targeted drugs such as sorafenib and immune drugs such as lizumab and PD-1 inhibitors. Long-term use of liver cancer drugs and chemotherapy can lead to side effects such as reduced immunity, liver function damage and reduced digestion. In recent years in vitro and in vivo experiments have shown that phytochemicals can alleviate these side effects. Chemotherapy with oxaliplatin in patients with hepatocellular carcinoma leads to diarrhoea and intestinal inflammation. Yu zhang et al. have shown that polysaccharide form *Lentinus edodes* alter the spatial structure of the intestinal flora in mice and exhibit intestinal anti-inflammatory activity in mice [140]. The combination thus attenuated the side effects produced by oxaliplatin induction. PHY906 is a kind of plant medicine derived from Huangqin decoction, which is composed of Scutellaria, licorice, peony and jujube. In recent years, several studies have found that PHY906 could enhance the efficacy of sorafenib and other drugs, and reduce their toxic and side effects [141–143].

8.2. Co-delivery nanomedicines for combination of chemotherapeutics and phytochemicals

A glycyrrhetinic acid-modified chitosan-cystamine-poly (ε-caprolactone) copolymer micelle was prepared for the co-delivery of doxorubicin and curcumin. Glycyrrhetinic acid modification significantly facilitate the cell uptake of micelles by hepatocellular cells through receptor-mediated endocytosis [144]. Co-delivery of ursolic acid and sorafenib in a pH-sensitive chitosan-conjugated mesoporous silica nanoparticle was prepared and showed promising results for hepatocellular carcinoma combinational therapy, especially for the hepatocellular carcinoma metastasis chemoprevention [145]. Silica nanoparticles decorated with pH sensitive chitosan exhibited pH-responsive function and sustained release of ursolic acid and sorafenib [145]. pH-responsive lactosylated nanoparticles composed of LAC-ADH-PEG-PCL materials showed more efficient release of sorafenib and curcumin in pH 5.5 than in pH 7.4 [146].

9. Breast cancer

9.1. Combination of chemotherapeutics and phytochemicals

9.1.1. Synergistic effect of combination therapy

Thymoquinone (TQ) is a main effective monomer isolated from black cumin that has been used for the treatment of hypertension, asthma, dysentery and eczema for thousands of years [147]. In addition, several studies have demonstrated its anticancer potential [148]. For example, the combination of TQ (6.25 μM, 12.5 μM and 25 μM) with paclitaxel (10 μg/mL), induced higher cytotoxicity to breast cancer cell 4 T1 *in vitro* [148]. Another study indicated that TQ combined with gemcitabine had synergistic apoptotic activity on breast cancer cells [149]. Moreover, the combined treatment of TQ with doxorubicin had a stronger inhibitory effect on the tumor growth of BALB/c mice subcutaneously injected with MDA-MB-231 cells than either drug alone [150].

Sulforaphane (SFN) is an isothiocyanate, mainly derived from cruciferous vegetables such as cabbage. In breast cancer, SFN sensitized human breast cancer cells to paclitaxel-induced apoptosis by down-regulating the NF-κB signaling pathway [151]. In an orthotopic breast cancer model, SFN enhanced the effect of adriamycin via inhibiting tumor growth. In addition, given a lower dose of doxorubicin (2.5 mg/kg), the tumor regression effect of doxorubicin and Sulforaphane combined treatment was significantly better than that of SFN or doxorubicin alone, indicating that the combination of SFN and doxorubicin could be used to reduce the dose of doxorubicin required for cancer treatment [152]. In another study, SFN combined with docetaxel showed a greater reduction in the tumor volume of triple-negative breast cancer (TNBC) (reduced by 92.5% compared to the control group) [153]. Moreover, SFN and 5-fluorouracil also had a synergistic effect in TNBC MDA-MB-231 cells by inducing premature senescence and autophagic cell death [154].

Epigallocatechin gallate (EGCG), the main polyphenol in green tea, shows diverse biological properties, particularly antibacterial, antiviral, antioxidant, anti-tumor, anti-arteriosclerosis, anti-vascular proliferation as well as anti-inflammatory effects [155]. EGCG may act synergistically with sunitinib in lung cancer and breast cancer because it can inhibit IRS/MAPK signal transduction induced by sunitinib [156].

Quercetin is a flavonoid compound widely present in plants and shows a multiple anti-tumor effect. Increasing evidence shows that quercetin combined with chemotherapy drugs has synergistic sensitization effect on cervical cancer, pancreatic cancer, prostate cancer, colorectal cancer, breast cancer as well as other cancers. In

breast cancer, quercetin enhanced the sensitivity of breast cancer cells to lonidamine treatment. Their combination may be a candidate for a novel strategy of treatment for breast cancer [157].

Resveratrol, SNK and Honokiol may also have synergistic effects in combination with chemotherapeutic agents in HCC. In breast cancer, resveratrol combined with doxorubicin effectively enhanced the effect of chemotherapy drugs by inhibiting autophagy [158]. Recent research have elucidated that SHK was able to sensitize breast cancer cells to paclitaxel treatment through inducing apoptosis as well as SHK plus paclitaxel prolonged animal survival and reduced tumor size in vivo than the vehicle treatment group [159]. Honokiol is a multi-target natural compound, which can suppress the proliferation, invasion and metastasis of tumors, and has synergistic sensitization effect [160]. In breast cancer, honokiol resensitized adriamycin-resistant breast cancer cells to adriamycin by downregulating mir-188-5p [161].

9.1.2. MDR resistance overcome by the combination of phytochemicals

Honokiol not only has synergistic sensitization effect, but also can reverse the drug resistance. Honokiol could overcome multidrug resistance by down-regulating P-glycoprotein level [162]. Honokiol improved the efficacy of DOX by inhibiting the expression of mucin 1 (MUC1) and multidrug resistance protein (MRP1) in breast cancer cells [163].

Several studies have shown that quercetin was especially relevant for gynecological cancers such as breast cancer. In breast cancer, multi-drug resistance (MDR) severely hinders the chemotherapy efficacy. The strategy of pretreating MDA-MB-231/mdr1 cells with quercetin and DOX overcame multidrug resistance [164]. Quercetin could also reverse the drug resistance of breast cancer to DOX under the condition of hypoxia and protect spleen cells from DOX cytotoxicity through downregulating the expression of hypoxia inducible factor-1(HIF-1) in cancer [165].

Elemene (β-Elemene) is a sesquiterpene extracted from *Curcuma wenyujin*, which is often used in the therapy of various cancers with no serious adverse effects. In the current years, numerous studies have elucidated that β-elemene can induce cell apoptosis, block cell cycle and restrain cell proliferation in various cancer types [166]. β-Elemene not only has synergistic sensitization effect, but also plays a unique role in reversing drug resistance. In breast cancer, β-elemene overcame the resistance of breast cancer to tamoxifen by remolding the expression of estrogen receptor α (ERα) [167], and changed the multidrug resistance of breast cancer by lowering drug resistance transmission via exosomes [168].

In addition, GA treatment improved the sensitivity of paclitaxel to MDA-MB-231 cells through down-regulating the SHH signaling pathway [169]. Shikonin (SHK) also reduced the drug resistance of MCF-7R breast cancer cells to tamoxifen treatment by targeting uc.57/BCL11A [170]. In breast cancer, the combination of UA and doxorubicin (DOX) can reverse the multidrug resistance of breast cancer cells by inhibiting P-gp function and destroying energy and related amino acid metabolism [171].

9.1.3. Side-effects suppression by the combination of phytochemicals

Adriamycin is an effective drug for breast cancer chemotherapy. However, its toxicity to cardiomyocytes limits its clinical application. Tanshinone IIA has antitumor activity in addition to its cardiovascular protective effects. Tanshinone IIA in combination with doxorubicin was synergistic and reduced side effects including weight loss, bone marrow suppression, cardiotoxicity, and nephrotoxicity [172]. In addition, Quercetin could not only reverse the drug resistance of breast cancer to DOX under the condition of hypoxia but also reduce the toxicity of DOX [165].

Anti-metabolites such as 5-FU have also been shown to be successful treatments for advanced breast cancer. However, they are often accompanied by serious side effects that may limit clinical treatment options. The addition of curcumin during 5-FU treatment has been shown to protect normal cells from the toxic effects of 5-FU and to improve the tolerance of normal cells to 5-FU [173].

9.2. Co-delivery nanomedicines for the combination of phytochemicals and chemotherapeutic drugs

Meng et al [174] encapsulated resveratrol and paclitaxel into liposome composite preparation and found that the composite liposome could effectively reverse the drug resistance of breast cancer cells to chemotherapy. Quercetin and paclitaxel co-loaded nanoparticles overcome the multidrug resistance of breast cancer by inhibiting the expression of P-gp protein [175]. Paclitaxel and quercetin co-loaded mesoporous silica nanoparticles decorated with chondroitin sulfate could reverse MDR in breast cancer and improve chemotherapy efficacy [176].

Poly (DL-lactide-co-glycolic acid) (PLGA) can encapsulate both hydrophilic and hydrophobic drugs. Combination of salinomycin and curcumin in PLGA nanoparticles was developed to achieve synergetic effect in treating malignant cancer, which are highly efficacious against breast cancer stem cells by inducing G1 cell cycle arrest and limiting EMT [177]. Methotrexate and curcumin co-encapsulated PLGA nanoparticles showed synergic effect on inhibiting the progression of breast cancer [178]. Sreeja Narayanan et al. co-encapsulated epigallocatechin gallate with paclitaxel in PLGA nanoparticles, which was able to sensitize breast cancer cells to paclitaxel [179,180]. PLGA nanoparticles loaded with tamoxifen and quercetin demonstrate higher oral bioavailability, improved breast cancer efficacy and reduced hepatotoxicity [181]. Active targeting PLGA nanoparticles with hyaluronic acid -modification loaded with docetaxel and quercetin could promoted cellular uptake and inhibited breast cell migration and invasion by initiating the Akt/MMP-9 signal pathway [182]. Multidrug resistance is one of the important difficulties in the clinical treatment of breast cancer. Resveratrol can increase intracellular chemotherapeutic drug accumulation by inhibiting p-glycoprotein activity, and it was co-encapsulated with doxorubicin in PLGA nanoparticles. Doxorubicin /resveratrol -loaded NPs mainly delivered the drugs to tumor tissue and significantly inhibited the doxorubicin -resistant breast tumor growth in tumor-bearing mice [183].

Combination therapy of curcumin and anticancer drugs could enhance the anti-cancer efficacy and decrease the side-effect. Co-administration of paclitaxel and curcumin prepared in a PEGylated lipid bilayer coated mesoporous silica nanoparticle allowed for efficient intracellular drug delivery with sustained release characteristics. In vivo results showed that this mesoporous silica nanoparticle could effectively accumulated in the tumor site and showed better anti-tumor effect and exhibit good targeting characteristics for breast cancer [184,185]. Gold nanocages with hollow interiors and adjustable local surface plasmon formants in the near-infrared region are often used for drug delivery. Co-delivery drug system based on Au nanocages for the combination of doxorubicin and quercetin exhibited fast release and strong cytotoxicity against MCF-7/ADR cells under NIR irradiation [186]. Carbon nanotube are a class of carbon nanostructures along with fullerenes. Conjugation of docetaxel to multiwalled carbon nanotube with further piperine absorption showed enhanced performance of docetaxel in cancer chemotherapy. It exhibits better antitumor activity in MCF-7 and MDA-MB-231 breast cancer cells [187]. Co-delivery of N-desmethyl tamoxifen and quercetin with the multiwalled carbon nanotube conferred the desired temporal drug delivery, enhanced drug efficacy, biocompatibility and conducive pharmacokinetics [188]. And reduced IC50 values and better cellular uptake in drug resistant MDA-MB-231 cells were observed.

10. Stomach cancer

10.1. Combination of chemotherapeutics and phytochemicals

10.1.1. Synergistic effect of combination therapy

Thymoquinone (TQ) significantly enhanced the anti-tumor effect of cisplatin-induced gastric cancer by inhibiting PI3K/AKT signaling pathway, activating mitochondrial pathway, up-regulating PTEN gene and down-regulating P-glycoprotein in vitro and in vivo [189]. In addition, thymoquinone also enhances 5-fluorouracil-induced apoptosis of gastric cancer cells and inhibits tumor growth by enhancing the activation of caspase-3 and Caspase-9 [190].

Licochalcone A (LCA) is a kind of flavonoids extracted from the root of licorice, which has anti-parasite, anti-bacterial and anti-tumor properties. LCA combined with 5-Fu may produce extensive anticancer effects on gastric cancer cells by up-regulating the levels of Bax, cleaved poly ADP ribose polymerase, tumor protein 53 and caspase-3 [191]. Synergistic breast cancer suppression efficacy could be observed by the combination of doxorubicin with glycyrrhetinic acid as an angiogenesis inhibitor [192].

In addition to the phytochemicals mentioned above, a number of other medicines derived from traditional Chinese medicine have been shown to have a synergistic effect in gastric cancer. Curcumin could improve the sensitivity of 5-FU to gastric cancer(GC) cells by down regulating COX-2 protein and NF-kB signaling pathways [193]. Pterostilbene enhances sorafenib's anticancer effects on gastric adenocarcinoma by arresting cells in G1 phase and inducing autophagy and promoting apoptosis [194]. Luteolin inhibits the proliferation of gastric cancer cells by blocking G2/M and promoting apoptosis, and synergizes with oxaliplatin via the Cyt c/caspase pathway, and also synergizes with cisplatin to inhibit the growth of gastric cancer cells [195,196]. Hesperetin can inhibit PI3K/AKT signaling pathway and induce mitochondrial apoptosis pathway by upregulating PTEN expression, thus significantly enhancing the killing effect of DDP on gastric cancer cells [197]. Doxorubicin in combination with curcumin in gastric adenocarcinoma enhanced anticancer potency [198]. Gambogic acid synergizes on human gastric cancer cell BGC-823 by regulating the metabolism of 5-fluorouracil [199]. Trastuzumab plus osthole exerted their synergistic effects mainly on AKT signaling pathway in gastric cancer [200]. Synergistic anti-tumor effect of schisandrin B and apatinib in vitro by inducing apoptosis [201]. Deguelin is a naturally occurring rotenoid with marked chemopreventive and antitumor activity. The combination of deguelin and cisplatin synergistically inhibits the proliferation of MGC-803 cells [202]. β-asarone is the main active ingredient of the Chinese herb *Rhizoma Acori Tatarinowii*, which exhibits a wide range of biological activities. It increases Chemosensitivity of cisplatin by inhibiting Tumor Glycolysis in Gastric Cancer [203]. Combined application of crocin and cisplatin can inhibit the growth of GC-823 cells and promote cell apoptosis. The combined treatment significantly increased the expression of p53 and Bax, and significantly decreased the expression of Bcl-2 [204]. Cucurbitacin E may enhance the antitumor effect of DOX in gastric cancer by inactivating AKT [205].

10.1.2. MDR resistance overcome by the combination of phytochemicals

Resveratrol is a nutraceutical compound that has exciting pharmacological potential to reverse chemoresistance in several cancer types. Resveratrol reversed doxorubicin resistance in gastric cancer by inhibiting EMT through regulating PTEN/Akt signaling pathway [206].

Gossypol is a yellow polyphenolic hydroxydi-naphthalene aldehyde compound, mainly present in the roots, stems, leaves and seeds of the mallow plant cotton, with the highest content in cottonseed kernels. Combination therapy with gossypol shows synergism against gemcitabine resistance in GC cells with high BCL-2 expression [207].

In addition to the above phytochemicals, cardamonin significantly reverses drug resistance of 5-FU in GC cells by the downregulated expression levels of P-glycoprotein, β-catenin and TCF4 [208]. EGCG reverses drug resistance to 5-FU in gastric cancer by inhibiting the TFAP2A/VEGF pathway and down-regulating the expression of resistance-associated genes MDR-1 and P-gp [209]. Aurora-A protein was up-regulated in response to cisplatin in gastric cancer cells SUN-688, and Aurora-A protein degradation and apoptosis were increased after capsaicin combined with cisplatin treatment, suggesting that capsaicin may overcome cisplatin resistance [210]. Chrysin can enhance the chemotherapeutic effect of 5-FU on gastric cancer AGS and AGS/FR cells by inhibiting the cell cycle. Therefore, chrysin may be used to treat gastric cancer that is resistant to 5-FU [211]. Bufalin reverses the resistance of gastric cancer cells to cisplatin by inhibiting the AKT signaling pathway and enhances the efficacy of cisplatin [212].

10.1.3. Side-effects suppression by the combination of phytochemicals

Phytochemicals can reduce the use of chemotherapy drugs and improve their efficacy, thus reducing the side effects produced by chemotherapy drugs. Combination of cisplatin and triptolide at lower concentrations induces apoptosis mediated by the mitochondrial pathway resulting in synergistic anticancer effects in gastric cancer. *Amauroderma rugosum* exhibited the protective role on doxorubicin-induced cardiotoxicity through suppressing oxidative stress, mitochondrial dysfunction, apoptosis, and activating Akt/mTOR and Nrf2/HO-1 signaling pathways [213]. Moreover, in the SCID mouse xenograft model, the combination therapy exhibited excellent antitumor effect and no obvious side effects [214]. Wogonin enhanced the antitumor effect of low dose 5-fluorouracil on gastric cancer by down-regulating NF-kappaB and regulating its metabolism to induce apoptosis [215]. When used in combination, Wogonin reduces the dose of oxaliplatin.Therefore, this is a related strategy to reduce the side effects of oxaliplatin while achieving the same response in human gastric cancer cells [216]. Co-treatment of gastric cancer cells with low-dose cisplatin and vitamin C can synergistically increase the cytotoxic effect of cisplatin. This may effectively reduce the side effects caused by cisplatin [217].

10.2. Co-delivery nanomedicines for the combination of phytochemicals and chemotherapeutic drugs

Nanomedicine offers many benefits in the diagnosis and treatment of cancer. Phytochemicals and chemotherapeutic drugs co-encapsulated with nanomedicines are currently being used in the treatment of gastric cancer. These nanomedicines can enhance the efficacy of the loaded chemotherapeutic drugs and reduce side effects, improving the effectiveness of gastric cancer treatment. Quercetin has shown different promising anticancer activities, and it can inhibit the multidrug resistance (MDR) family members, such as P-gp, which are responsible for the efflux and recognition of chemical drugs. Co-delivering of quercetin with doxorubicin in a hyaluronic acid (HA)-modified silica nanoparticle was able to decreased the expression of P-gp Wnt16, thus reshaping tumor microenvironment, reversing multidrug resistance and promoting doxorubicin activity [218]. Lijun Pang et al. prepared reactive oxygen species (ROS)-responsive nanococktail (PCM) with self-amplified drug release [219]. Chlorin e6 and triptolide were co-loaded in a pH-sensitive supramolecular nanosystem for chemo-photodynamic combination therapy [220]. The nanoparticles

reduce side effects and greatly increase the therapeutic efficacy of the drug.

11. Pancreatic cancer

11.1. Combination of chemotherapeutics and phytochemicals

11.1.1. Synergistic effect of combination therapy

Genistein is a soy-derived isoflavone with a variety of pharmacological activities that can have a synergistic effect with chemotherapeutic agents. The combination of 5-FU and genistein significantly reduces final xenograft tumor volume by inducing apoptosis and autophagy compared to 5-FU alone, and confirms that genistein can be used as an adjuvant therapy for pancreatic cancer [221].

6-Shogaol, a bioactive ingredient of ginger root (Zingiber officinale), is a medicinal plant having anti-inflammatory, and anti-carcinogenic properties and a carminative effect. The combination of 6-shogaol and gemcitabine enhances the therapeutic effect of gemcitabine by modulating TLR4/NF-kappaB signaling [222].

Shikonin (SK) induces apoptosis and necrosis of different types of pancreatic cancer cells by regulating the expression of RIP1 and RIP3, thus enhancing the efficacy of gemcitabine in vitro and in vivo [223]. Similarly, thymoquinone and gemcitabine combined therapy can inhibit notch1, PI3K/Akt/mTOR regulated signaling pathways, and synergically induce increased apoptosis and tumor growth inhibition in pancreatic cancer cells in vivo and in vitro [224].

In addition to genistein, 6-Shogaol and shikonin, triptolide synergistic with DDP can reduce cell viability and induce apoptosis through mitochondrial pathway, and improve sensitivity of pancreatic cancer to cisplatin (DDP) by down-regulating heat shock protein 27 (HSP27) [225]. In pancreatic cancer, gemcitabine (GEM) is the first approach for anticancer treatment. Quercetin was shown to improve GEM to sensitivity of pancreatic cancer cells by inhibition of the receptor for advanced glycation end products (RAGE) expression [226]. Resveratrol increases the intracellular accumulation of DOX by downregulating P-glycoprotein in 2D monolayers and 3D spheroids in PANC-1 cells [227]. Triptolide synergistically increases gemcitabine-induced cell proliferation inhibition and apoptosis by modulating BCL-2 and mitochondrial membrane potential in pancreatic cancer cells [228]. EGCG sensitizes gemcitabine by downregulating ERK phosphorylation and reduces pancreatic cancer cell growth in a concentration- and time-dependent manner [229]. Curcumin in combination with celecoxib may enhance the therapeutic effect of celecoxib in pancreatic cancer by inhibiting COX-2 [230]. In an orthotopic model of pancreatic cancer, luteolin combined with gemcitabine significantly reduced tumor mass while increasing cytochrome *c* expression and caspase activation [231]. The combination of apigenin and gemcitabine inhibits pancreatic cancer cell growth by cell cycle arrest, down-regulation of P-Akt, and induction of apoptosis [232].

11.1.2. MDR resistance overcome by the combination of phytochemicals

Cyclopamine is an isosteroidal alkaloid isolated from *Veratrum genus*, which mainly exists in Liliaceae plants. It has significant inhibitory activity on basal cell tumor, glioma, small cell lung cancer, gastric cancer, breast cancer and other malignant tumors, and is a potential anti-tumor drug. Inhibition of the hedgehog pathway by cyclopamine is an effective approach to reverse gemcitabine resistance in pancreatic cancer in PDAC [233].

In addition, quercetin could reverse the resistance of pancreatic cancer cells to daunorubicin by inhibiting the expression of P-glycoprotein (P-gp) expression [234]. The receptor for advanced glycation end products (RAGE) mediated gemcitabine (GEM) resistance to pancreatic adenocarcinoma, thus UA can reverse resistance by inhibiting the expression of RAGE [235].

11.1.3. Side-effects suppression by the combination of phytochemicals

For patients, reducing the dose of chemotherapy drugs is also an effective way to reduce side effects. Some low-toxic phytochemicals enhanced the tumor-suppressive effect of low-dose chemotherapeutics, although failed to synergistically induce cell death. Low concentrations of sorafenib in combination with betulinic acid synergistically inhibit the proliferation of PDAC cells and suppress their monoclonal activity [236].

11.2. Co-delivery nanomedicines for the combination of phytochemicals and chemotherapeutic drugs

Betulinic acid is a pentacyclic triterpenoid extracted from birch tree. It has anti-tumor, antiviral and anti-inflammatory activities, and is famous for its anticancer activity [237]. Gemcitabine and betulinic acid co-encapsulated PLGA-PEG polymer nanoparticles are more effective in inhibiting tumor growth in solid tumor models compared with the direct mixing and administration of the two drugs at the same concentration [238].

Considering the poor water solubility and low bioavailability of curcumin in vivo, Khan S et al. developed a non-toxic, highly bioactive nanoformulation. In an orthotopic mouse tumor model, Superparamagnetic iron oxide nanoparticle (SPION) formulation of curcumin (SP-CUR) efficiently delivered bioactive curcumin to pancreatic tumors while enhancing gemcitabine uptake and its efficacy [239].

Using chitosan-coated solid lipid nanoparticles to encapsulate Ferulic acid and aspirin co-delivery in a mouse model of xenograft tumors, the tumor volume was significantly reduced [240].

12. Other cancers

12.1. Combination of chemotherapeutics and phytochemicals

12.1.1. Synergistic effect of combination therapy

Phytochemicals can also have a synergistic effect in other cancers. In glioblastoma, TQ combined with temozolomide has synergistic killing effect on U87MG cells and significantly reduced the invasion of U87MG cells [241]. In human urothelial carcinoma, honokiol significantly enhanced the cytotoxicity of 5-FU and showed a synergistic effect with 5-FU in Urothelial Cell Carcinoma cells [242]. In malignant glioma, honokiol enhanced the apoptosis induced by temozolomide through a mitochondrial dependent mechanism and reduced the side effects caused by temozolomide [243]. Honokiol was also showed to reverse the resistance of multiple myeloma to bortezomib by inducing caspase-dependent and independent apoptosis [244]. In oral squamous cell carcinoma, honokiol combined with 5-FU had synergistic killing effect by inducing apoptosis through mitochondria mediated endogenous pathway [245]. In Hodgkin's lymphoma, the clinical application of doxorubicin usually leads to severe cardiotoxicity and the development of multi-drug resistance. The combination of curcumin and doxorubicin is more effective in reducing the proliferation of Hodgkin's lymphoma cells [246]. In retinoblastoma (RB), curcumin improved the sensitivity of RB cells cope with chemotherapeutic drugs, thereby enhancing the anti-cancer effect [247]. In prostate cancer, the combination of SFN and paclitaxel was used to treat prostate cancer cell DU145 and showed that SFN enhanced antitumor effects of low-dose paclitaxel [248]. In addition, curcumin could improve the sensitivity of prostate cancer cells to docetaxel by inducing apoptosis [249]. In renal cancer, resveratrol increased

the sensitivity of renal cancer cells to paclitaxel by inhibiting the expression of survivin through PI3K/Akt signaling pathway [250]. SFN could also enhance its cytotoxicity when used in combination with other anti-myeloma drugs. For example, SFN possessed synergistic treatment effects on bortezomib and conventional drugs such as doxorubicin, dexamethasone as well as melphalan [251]. Epigallocatechin gallate was illustrated to efficaciously suppress tumor cells growth in biliary tract cancer (BTC). In addition, Epigallocatechin gallate displayed a synergistic effect with cisplatin in the most tested biliary tract cancer cell lines [252]. In cervical cancer, quercetin pretreatment sensitized HeLa cells to cisplatin-induced apoptosis in HeLa cells [253]. Elemene (β-Elemene) is a sesquiterpene extracted from *Curcuma wenyujin*, which is often used in the therapy of various cancers with no serious adverse effects. In the current years, numerous studies have elucidated that β-elemene can induce cell apoptosis, block cell cycle and restrain cell proliferation in various cancer types [166]. In bladder cancer, β-elemene nanoliposomes could enhance the efficacy of cisplatin on bladder cancer [254]. In addition, β-elemene promotes cisplatin-induced apoptosis of bladder cancer cells through ROS-AMPK signaling pathway [255]. In ovarian cancer, co-treatment with paclitaxel and β-elemene induced apoptosis of ovarian cancer cells and inhibited the growth, migration, invasion through STAT-NF-KB signaling pathway [256].

12.1.2. MDR resistance overcome by the combination of phytochemicals

In bladder cancer, the effect of cisplatin is limited with the development of cell resistance. Co-treatment with curcumin and cisplatin synergistically induced apoptosis through reactive oxygen species (ROS)-mediated activation of extracellular regulated kinase (ERK)1/2 in bladder cancer [257]. In bladder cancer, chemoresistance to cisplatin is the main cause of treatment failure and death in advanced bladder cancer (BC). SHK was found to be sensitive to cisplatin-resistant cells. The combination of SHK and cisplatin could significantly reduce the growth and metastasis of BC [258]. In cervical cancer, curcumin can reverse the resistance of cancer cells to cisplatin by inhibiting the expression of P-gp1 and MRP1 [259]. Furthermore, quercetin reversed paclitaxel resistance in prostate cancer by down regulating androgen receptor and inhibiting PI3K/Akt pathway [260]. In addition, quercetin could down regulate the expression of deltaNp73 and reverse the resistance of melanoma to temozolomide [261].

12.1.3. Side-effects suppression by the combination of phytochemicals

The combination of honokiol and 5-fluorouracil (5-FU) can synergistically stimulate oral squamous cell carcinoma (OSCC)cell apoptosis and did not increase the toxicity of 5-FU in vivo and in vitro [245].

Docetaxel has been clinically approved and is widely used to treat metastatic castration-resistant prostate cancer. However, long-term use of docetaxel treatment may cause serious toxicity to patients [262]. The combination of docetaxel and curcumin significantly inhibited the proliferation of prostate cancer cells, reduced the therapeutic dose of docetaxel, and decreased the toxicity [249].

12.2. Co-delivery nanomedicines for the combination of phytochemicals and chemotherapeutic drugs

JUN HU et al. prepared a type of DSPE-PEG2000 polymeric liposomes containing temozolomide and quercetin, which displayed an antitumor effect both in the U87 cells and the TMZ-resistant U87 (U87/TR) cells. In vivo distribution experiment showed obvious accumulation of the liposomes in the brain, plasma concentrations of temozolomide and quercetin are significantly increased, and clearance is delayed in glioma rat model [263].

Yuzhu Hu et al. [264] co-loaded docetaxel and curcumin in the biodegradable MPEG-PLA copolymer nanomicelles (DTX-Cur/M). The obtained micelle with an average particle size of 37.63 nm. In vivo experiments showed that the DTX-Cur/M is the most effective treatment for ovarian cancer by promoting tumor apoptosis, inhibiting tumor proliferation as well as suppressing tumor angiogenesis.

The low drug-loading capacity of traditional micelles is typically less than 10% (w/w), resulting from the large amount of carrier necessary to stably encapsulate the drug. This leads to an increased delivery of therapeutically inactive carrier excipients and can cause carrier-induced toxicity. The group of Prof. Motoichi Kurisawa has pioneered the designed nanocarriers comprised of the anticancer agent EGCG [265]. Sunitinib-loaded micellar nanocomplex (SU-MNC) was further developed by using poly (ethylene glycol)-conjugated epigallocatechin-3-O-gallate (PEG-EGCG) as the carrier, wherein the EGCG and SU moiety formed a hydrophobic core surrounded by a hydrated PEG shell. The SU-MNC demonstrated significantly superior synergistical efficacy as well as tumor-targeted delivery facilitated by the carrier [266].

Jian-Tao Lin et al. designed a pH and redox dual-stage responsive mesoporous silica nanoparticles system for co-delivery phosphorylated curcumin with doxorubicin, which allowed for long time duration in blood circulation, improved cell uptake when the cationic hydrogel coating was exposed, and drug release inside in Hela cells [169]. Mesoporous silica nanoparticle was further developed as drug carriers to investigate the effects of curcumin and 5-fluorouracil on Hep-2 laryngeal cancer cells, which produced a synergistic effect on tumor growth [267].

In the past few decades, gold nanoparticles (AuNPs) have become highly feasible materials in the field of clinical diagnostics, biomedical imaging, and drug delivery owing to their unique stability, biocompatibility and significant surface modifiability. Gheorghe Tomoaia et al. synthesized a gold nanoparticle capped with resveratrol, which was further complexed with doxorubicin (Dox-GNPs). The Dox-GNPs complexes showed a strong accumulation inside the cancer cells and can be developed as potential drugs for cervical cancer therapy [268]. In addition, Epigallocatechin gallate and gelatin-doxorubicin conjugate coated gold nanoparticles could effective accumulation in PC-3 cells by receptor-mediated endocytosis and significantly inhibit of the prostate cancer cells proliferation [269].

13. Clinical study on combined treatment of phytochemicals and chemotherapeutic drugs

Prolonged treatment with chemotherapeutic agents during clinical therapy can be limited by lack of efficacy, drug resistance, metastasis and severe side effects, ultimately leading to poor patient outcomes. In recent years, a lot of basic research has been conducted on phytochemicals and the results have shown that they have pharmacological activities such as inhibiting the proliferation, migration and invasion of cancer cells and promoting apoptosis. The combination of chemotherapeutic drugs and phytochemicals has shown promising results in cancer treatment. The combination of chemotherapeutic drugs and phytochemicals has been shown in numerous basic studies to enhance the efficacy of chemotherapeutic drugs, reverse multidrug resistance and reduce side effects. Clinical studies have also demonstrated that the combination of chemotherapeutic drugs and phytochemicals produces better therapeutic results.

Curcumin, a plant-based natural polyphenol, has proved to be a promising anticancer drug. Masashi Kanai et al. evaluated the

safety and feasibility of oral curcumin combined with gemcitabine chemotherapy. A phase Ⅰ/Ⅱ study in patients with pancreatic cancer showed that oral administration of 8 g curcumin daily in combination with gemcitabine is safe and feasible [270]. Mathilde Bayet-Robert et al. conducted a phase Ⅰ trial of docetaxel combined with curcumin in patients with advanced and metastatic breast cancer [271]. After the combination of docetaxel and curcumin, some improvement was observed in the majority of patients, showing good efficacy. In single centre, single arm prospective phase II trial, curcumin in complexed form with phospholipids (Meriva®) can be used in the treatment of PC as a complementary therapy to GEM. With an overall disease control rate of 61.4% in 52 patients, adjuvant therapy with curcumin and gemcitabine combination was not only safe but also showed good response rates in the first-line treatment of advanced pancreatic cancer [270,272].

β-Elemene has been successfully isolated from the natural zingiberaceae plant wenyujin, a small molecule with high efficiency and low toxicity. β elemene prevents chemotherapy-induced bone marrow suppression and increases interleukin-2 production. In this retrospective study, patients treated with β -elemene produced lower toxicity and significantly improved outcomes in patients with esophageal squamous carcinoma [273].

14. Current challenges and perspectives

We analyze the pros and cons of various oncology therapies in terms of the future prospects of oncology treatment with chemotherapeutic drugs combined with phytochemicals in nano-co-delivery systems. We also present the current challenges of such combinations.

The incidence and mortality of cancer are increasing year by year, and currently our main treatments for tumors include, surgery; chemotherapy; radiation therapy; targeted therapy; biotherapy; immunotherapy; and gene therapy. Surgical surgery is the most effective means to treat solid tumors, but the choice of surgery has certain feasibility and contraindications, and the size, location and relationship of adjacent tissues of the tumor need to be considered. For tumors that are not easily resected, cancer cells can easily spread through blood vessels and lymphatic vessels during surgery. Therefore, in clinical practice, most patients with mid- to late-stage cancer are treated with conservative radiotherapy and chemotherapy. For breast cancer, head and neck tumor, melanoma, nasopharyngeal cancer, lung cancer, etc., radiotherapy can be considered in light of the actual situation. Generally speaking, radiotherapy will not only kill the cancerous tissues, but also affect the paracancerous tissues and cause some damage to the normal tissues. Chemotherapy is the most common treatment modality. Although oxaliplatin, cisplatin, 5-FU, gemcitabine, and other common clinical first-line chemotherapeutic drugs can significantly improve the cure rate, they also bring side effects that cannot be ignored. Chemotherapeutic drugs are not selective in killing cancer cells, and they kill a large number of normal cells while killing cancer cells. Therefore, for this indiscriminate attack, targeted drugs have been derived. Targeted drugs are developed to target tumor genes and can identify specific loci of tumor cell specific genes, such as cetuximab which targets EGFR and Trastuzumab which treats HER2-positive, so these drugs have the characteristics of killing tumor cells efficiently and accurately, and have less side effects than conventional chemotherapy. However, targeted drugs are only applicable to those cancer cells that have mutated genes and produced specific proteins, and when such drugs are used for a long period of time, they can produce drug-resistant effects, which is a rather difficult problem in tumor treatment. Immunotherapy and gene therapy are newly emerged tumor treatments in recent years. Immunotherapy is to achieve anti-tumor effects by regulating the immune function of the body. Gene therapy refers to the introduction of exogenous normal genes into the target cells, in order to correct or compensate for the diseases caused by defective and abnormal genes, in order to achieve therapeutic purposes. At present, immunotherapy and gene therapy cover a small area in clinical application, the technology is relatively not very mature, contains some uncertain risks, and is selective for the type of cancer to be treated and more expensive. According to the advantages and disadvantages of these treatments, two or two combinations or multiple treatments are applied simultaneously to complement each other's strengths and weaknesses and strive to cooperate to achieve the best efficacy. From the initial combination of radiotherapy to multiple chemotherapy drugs combined with each other to chemotherapy drugs combined with phytochemicals, various combinations of treatments are emerging, and even more so with chemotherapy combined with immunotherapy and chemotherapy combined with gene therapy. The challenge of current cancer treatment is the lack of the most effective, least toxic, and most precise means. Currently, chemotherapeutic drugs still dominate clinical practice, so the lack of efficacy or toxic effects of these drugs should be addressed. In recent years, the excellent antitumor effects of phytochemicals have gradually emerged as adjuvant therapeutic agents to chemotherapeutic drugs with their multi-targeting and mild effects. The combination of chemotherapeutic drugs with phytochemicals is a promising oncology treatment from the viewpoint of economy and safety and efficacy. Based on the chemotherapeutic drugs already widely used in clinical practice, it achieves the results of increasing the effectiveness, reducing the toxicity and overcoming the resistance of tumors, which is undoubtedly of great help to every patient.

No matter what kind of treatment is used to treat cancer, our ultimate goal is to achieve the desired therapeutic effect and reduce the patient's pain. As most chemotherapy drugs have single target, poor side effects, insufficient efficacy and drug resistance. The limitations of chemotherapeutic drugs increase the difficulty of tumor treatment. In contrast, phytochemicals have multi-component, multi-target and multi-stage characteristics, and therefore show great advantages in the treatment of tumors [274].

The anti-tumor potential of phytochemicals is increasingly highlighted through basic research. It was found that most phytochemicals exhibit lower toxicity in vivo and in vitro compared to chemotherapeutic drugs, so researchers have tried to combine phytochemicals with chemotherapeutic drugs to treat cancer, and in the basic research stage, it was found that this combination means achieved good efficacy, not only synergistically increasing the sensitivity of chemotherapeutic drugs to tumors, but also reversing tumor resistance and reducing the dose of chemotherapeutic drugs used. Most combination therapies have been developed empirically, and few experimental studies have aimed to thoroughly explore different drug combinations using appropriate analytical methods. However, the study of drug metabolic processes and biological interaction patterns in preclinical models, as well as the timing, will influence the final clinical outcome of combination therapies. In particular, the combination of phytochemicals with chemotherapeutic agents requires consideration of the stability of the combination and the detailed mechanisms of multidrug antitumor effects, which are pressing issues. Drug combinations may also produce antagonistic effects, where the combined effect is inferior to that of a single drug, for example, where one drug counteracts the effect of another drug. Therefore, control of the dose and chronological sequence of administration of each combination of drugs requires precise control of the form of administration. To obtain the ideal combination of drugs. Of course considering the water solubility,

bioavailability, and stability of most phytochemicals, researchers have adopted the use of nanocarriers to load phytochemicals, which can effectively solve these problems. The combination of nanomedicines and phytochemicals can further improve therapeutic efficacy, overcome drug resistance, and reduce side effects. Nanoscale drug delivery systems have been developed for dual/multi-drug co-delivery, such as liposomes, micelles, supramolecules, dendrimers, host–guest supramolecules, and inorganic systems [275]. Today there are fewer reports on multidrug nanocodelivery for cancer treatment in the clinical setting and there are still some challenges that hinder therapeutic efficacy and clinical translation. In clinical use, safety, allergic reactions, drug interactions, mechanism of action, and biosafety of nanomaterials need to be considered, and only when these issues are fully addressed will this combination therapy become widely available in the clinic. Chemical substances extracted from plants with low economic efficiency, low toxic reactions, and high anti-tumor activity are used as an adjuvant therapeutic drug to chemotherapeutic drugs, combined with targeted delivery and on-time on-demand drug release by nano drug delivery systems. This combination therapy can complement each other's strengths and weaknesses, and we believe that with further refinement by researchers, it has the promise to shine in the clinical setting and bring a boon to cancer patients.

15. Conclusions

The occurrence and development of malignant tumor are multi-step, multi-factor accumulation process as well as the number of cases and mortality rate are increasing year by year. Therefore, cancer therapy still remains a major challenge so far. Currently, surgery is the main treatment, supplemented by chemotherapy. But chemotherapy has many disadvantages, such as insufficient efficacy, drug resistance, metastasis, and undesirable side effects, and so on. Compared with traditional single chemotherapeutic therapy, combination therapy based on phytochemicals and chemotherapeutic drugs can achieve the best therapeutic effect through synergistic antitumor effect. Over the past few decades, this combination of cancer therapy has made rapid progress. In order to realize the maximized combination advantages of small-molecule chemotherapeutic drugs and natural compounds, a variety of functional nano-scaled drug delivery systems, such as liposomes, micelles, supramolecules, dendrimers, host–guest supramolecules. In addition, synergistically delivered nanomedicines based on the combination of phytochemicals and chemotherapeutic agents often have multiple functions, such as targeting accumulation in tumor tissues, controlling drug release, enhancing bioavailability, protecting unstable therapies, and responsive drug release triggered by internal and external stimuli.

With the deepening of the understanding of tumor molecular mechanism and the development of multifunctional co-delivery nano drugs, the combination of phytochemical drugs and chemotherapy drugs provides a new opportunity for anti-tumor therapy. Currently, based on the research of phytochemicals and chemotherapeutic drugs, a new strategy of combining phytochemicals and chemotherapeutic drugs against cancer will be established to achieve more efficient cancer treatment.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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