REVIEW
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Natural product-induced oxidative stress-synergistic anti-tumor effects of chemotherapeutic agents

Shu-Fan Wang[1], Shi-Qi Dong[1], Quan Dong[1], Wen-Xin Lin[1], Mei Dong[1], Duo Liu[1*]

[1]Department of Pharmacy, Harbin Medical University Cancer Hospital, Harbin 150086, China.

[*]**Correspondence to:** Duo Liu, Department of Pharmacy, Harbin Medical University Cancer Hospital, No. 150 Haping road, Nangang District, Harbin 150086, China. E-mail: liuduo95@126.com.

Author contributions

Liu D designed the study and revised the manuscript for important intellectual content. Wang SF, Dong SQ, and Dong Q performed the literature search. Dong SQ and Lin WX generated the figures and tables. Wang SF and Dong Q performed the background research. Wang SF drafted the manuscript. Liu D and Dong M edited the manuscript. All authors have read and approved the content of the manuscript.

Competing interests

The authors declare no conflicts of interest.

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Abbreviations

ROS, reactive oxygen species; THF, 3,5,7-Trihydroxyflavone; MH, 4-O-Methylhonokiol; WA, withangulatin A; CuB, cucurbitacin B; DHA, dihydroartemisinin; DET, deoxyelephantopin; GEM, gemcitabine; CRC, colorectal cancer.

Citation

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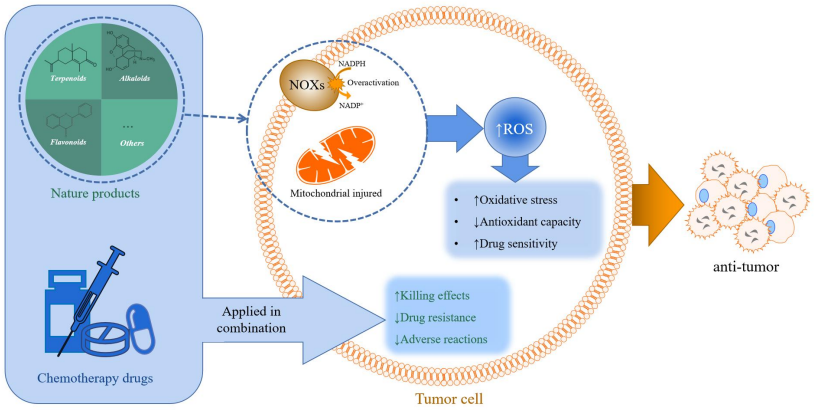
Abstract

Reactive oxygen species are closely related to tumor development. In recent years, reactive oxygen species has become a hot spot in tumor therapy, and many natural substances in nature contain compound components with anti-tumor effects. However, there is a lack of discussion on the synergistic anti-tumor effects of natural products in combination with chemotherapeutic drugs through reactive oxygen species. The terms “natural products”, “reactive oxygen species”, “anti-tumor”, and “chemotherapy” were used to identify the synergistic effects of natural products. We conducted a systematic literature search in PubMed and Web of Science databases for relevant research articles and reviews published in recent years. We systematically summarized the studies related to anti-tumor active ingredients in natural compounds in the field of reactive oxygen species in recent years. A total of 77 relevant literatures were included. Among them, 45 literatures containing various natural products such as terpenoids, flavonoids, alkaloids, etc. exert anti-tumor effects by regulating reactive oxygen species levels, and 32 literatures regarding adjunctive role of natural products in anti-tumor therapy. In this study, we found that natural products exert anti-tumor effects by elevating reactive oxygen species levels. It provides strong theoretical support for future clinical studies.

Keywords: nature products; tumor; reactive oxygen species; combination chemotherapy; oxidative stress



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Highlights

The natural product could regulate the level of cellular ROS.
The increase of ROS level play anti-tumor effect.
Natural products play anti-tumor roles in cooperation with chemotherapy drugs.

Medical history of objective

During the Spring and Autumn and Warring States Periods (770 B.C.E - 221 B.C.E), *Huangdi Neijing* had already recorded the symptoms of various types of tumors and the reasons for its formation, and believed that diseases caused by the accumulation of various factors due to the impassability of qi, blood, meridians and collaterals (poor circulation of blood and body fluids) are tumors. Herbal medicine plays an important role in anti-tumor, and natural products are the active ingredients of herbal medicine. For example, Lei Gong Teng Methylin is a natural product with a variety of biological activities derived from the root of Lei Gong Teng, which was first recorded in *Gleanings from the Compendium of Materia Medica* (1765 A.D.), and is known for its ability to activate the blood and open up the channels (promote blood circulation). Piperine is a biologically active ingredient derived from peppercorns. The history of pepper as a medicine was recorded in the *Tang Xinxiu Ben Cao* (659 A.D.), where it has the effect of warming the middle and dispersing cold (Chase away the cold).

Background

Cancer is currently a major global public problem, with recent statistics indicating that there will be approximately 19.3 million cancer cases and nearly 10 million cancer deaths worldwide in 2020 [1]. In particular, chemotherapy plays an essential role in the treatment of advanced cancer patients in the treatment of the disease. With the advance of basic and clinical research, it has been observed that traditional Chinese medicine has been surprisingly effective in anti-tumor treatment compared with the commonly used western chemotherapy [2]. After studies of the relevant genome and metabolomics, it is known that oxidative stress caused by reactive oxygen species (ROS) is a key factor in the development of tumorigenesis [3–5].

Mitochondria in cancer cells are characterized by overproduction of ROS, which promote cancer development by inducing genomic instability, modifying gene expression and participating in signaling pathways [6]. Researchers have also found that various natural products can exert anti-tumor effects by modulating ROS levels, and such studies have been summarized in recent years. Qian analyzed the role of herbal ingredients in cancer by modulating ROS levels [7]. Gaikwad provides a review from the perspective of plant compounds and further discusses their effects on ROS homeostasis in cancer [8]. Furthermore, some reviews related to the anti-tumor effects of natural products through elevated ROS are mentioned, which have different focuses and guide the subsequent studies from different directions [9–11]. However, the synergistic anti-tumor aspects of natural products in combination with chemotherapeutic agents through the ROS pathway have not been focused. Therefore, in this review we review the latest research on the use of natural products against tumors and further discuss the mechanisms by which they exert anti-tumor effects in combination with chemotherapeutic agents, and the role of elevated ROS levels in the regulation of cell signaling pathways. This will guide the development of clinical studies and provide more effective therapeutic strategies for tumor patients to realize the potential of natural products for tumor treatment.

The relationship between ROS and tumor development

Reactive oxygen species are a class of small molecules with high oxidative activity formed by oxygen atoms, including mainly superoxide anions ($O_2^{\cdot-}$), hydroxyl radicals (·OH) and hydrogen peroxide (H_2O_2) [12]. The imbalance between its production and antioxidant defense can cause cellular damage and apoptosis, causing disturbance of the normal metabolism of the body, thus leading to the development and progression of diseases [13].

ROS plays an important role in intracellular signal transduction pathways, regulates normal cellular physiological activities, and plays a dual biological role in tumor development [14]. A small amount of ROS may promote normal cell division and blood vessel formation, while the content of ROS in tumor cells is higher than that in normal tissue cells. While promoting proliferation and division, the oxidative stress increases, thus elevating ROS sensitivity, which further raises the level of ROS through positive feedback regulation until it exceeds the tolerated threshold and finally induces apoptosis [13].

Including impaired mitochondrial function, over-enhanced NADPH oxidase activity and other reasons to generate ROS beyond normal tissue cells will activate MAPK and extracellular signal-regulated kinase 1/2 (ERK1/2) and other related enzymes to regulate NF-κB, AKt and other signaling pathways to enhance cell proliferation, increase cell growth, cell survival and cancer development (Figure 1) [14].

Currently the most commonly used chemotherapeutic drugs, such as cisplatin and gemcitabine (GEM), can achieve anti-tumor effects by directly or indirectly inducing ROS production and promoting apoptosis and autophagy [15, 16]. It has also been found that non-chemotherapy drugs such as metformin can also exert anti-tumor effects by modulating ROS levels and have potential for clinical application [17]. However, the conditions of use are limited due to the serious adverse effects such as liver and kidney function damage and neuropathy caused by prolonged application. In recent years, researchers have discovered that natural active ingredients extracted from plants, animals and microorganisms can also induce ROS production and have anti-tumor activity. These natural products have the advantages of high efficiency, low toxicity and multi-target.

Natural products exert anti-tumor effects by regulating ROS levels

It has been suggested that natural products may exert anti-tumor effects by increasing oxidative stress or decreasing antioxidant defenses within tumor cells, interfering with redox homeostasis within tumor cells, and enhancing the sensitivity of tumor cells to oxidative stress from chemotherapy or radiotherapy [18, 19]. Natural compounds are increasingly involved in the field of cancer prevention and treatment. The natural compound composition is extensive and includes a wide variety of flavonoids, terpenoids, alkaloids, quinones, saponins and other compounds which can modulate ROS levels through different signaling pathways and exert anti-tumor effects (Figure 2).

It has been found that certain conventional chemotherapeutic agents not only elevate ROS in tumor cells leading to apoptosis, but also elevate ROS levels in normal cells up to the threshold for apoptosis, which can cause damage to normal cells with high proliferative capacity [20]. To address this situation, Mohammad used the natural product hesperidin, which can elevate intracellular ROS levels, to conduct experiments. In his study, hesperidin was applied to MCF-7 and MDA-MB-231 cancer cells as well as MCF-10A normal cells with different dosages and exposure times to analyze the effects of the ROS generated on cancer cells and normal cells. The results showed that the damaging effect of ROS on normal cells was weaker than that on tumor cells [21].

Terpenoids

Terpenoids are a group of naturally occurring hydrocarbons that are widely present in plants and can be isolated from a variety of plants. Previously, Abu-Izneid selected sesquiterpene compounds and their derivatives for review and elaborated on their specific mechanisms of anti-tumor activity [22]. Thus, based on the previous summary generalization, we further discuss the effect of terpenoids on different types of tumor cells through the ROS pathway.

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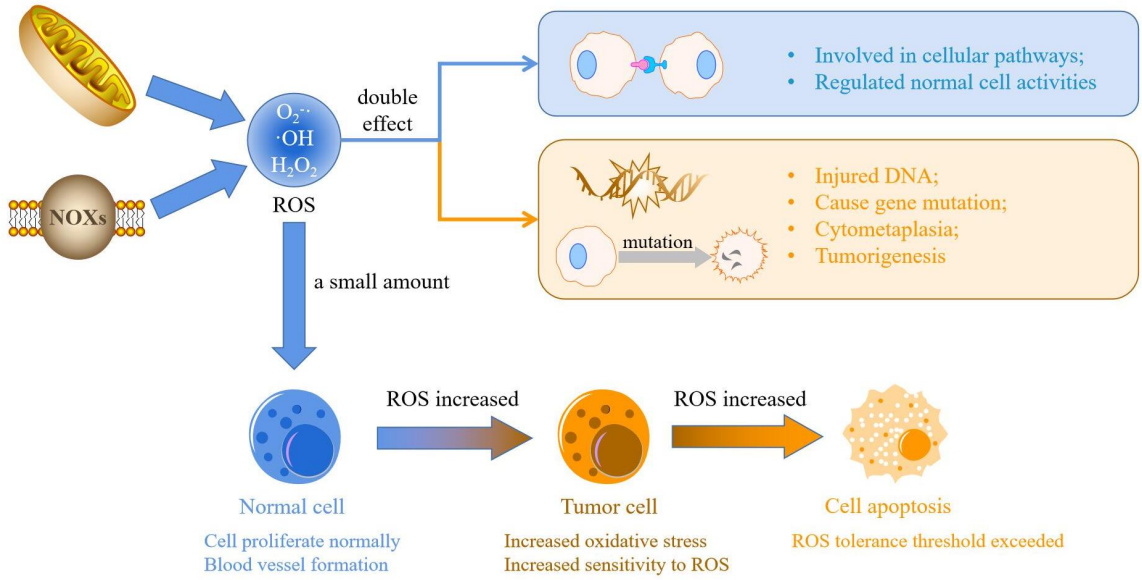

Figure 1 Production of ROS and its biological effects. ROS is a class of small molecules with high oxidative activity mainly composed of $O_2^{\cdot-}$, ·OH, and H_2O_2, NOXs and mitochondria are the main sources of ROS. ROS has dual biological activities: on the one hand, it participates in intracellular signaling pathways and regulates normal physiological activities of cells; on the other hand, it can injure DNA and cause gene mutation, which in turn leads to cell mutation and induces tumorigenesis. A small amount of ROS can promote normal cell division and blood vessel formation, while the content of ROS in tumor cells is higher than that in normal tissue cells. While promoting proliferation and division, oxidative stress increases, making its sensitivity to ROS also increases, which further raises the level of ROS through positive feedback regulation until it exceeds the threshold that cells can tolerate and finally induces apoptosis. ROS, reactive oxygen species; NOXs, NADPH oxidase.

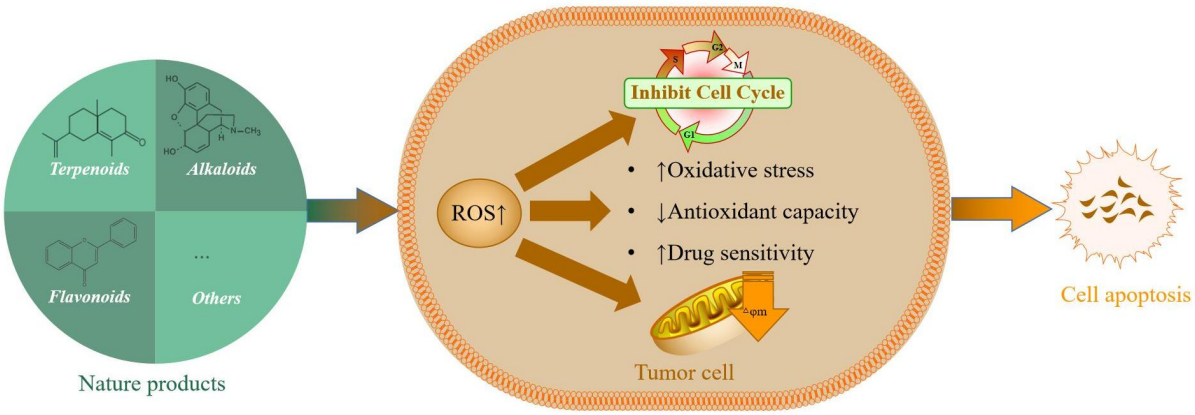

Figure 2 Natural products exert anti-tumor effects by regulating ROS levels. The natural products can increase the level of ROS in tumor cells to increase the oxidative stress in tumor cells, reduce their antioxidant defense capacity, interfere with the redox balance in tumor cells, enhance the sensitivity of tumor cells to the oxidative stress of chemotherapy or radiotherapy, and cause cell cycle block and decrease the mitochondrial membrane potential △φm, which in turn causes apoptosis and exerts anti-tumor effects. ROS, reactive oxygen species.

Colorectal cancer. Colorectal cancer is one of the most common malignancies worldwide, and is extremely malignant. An increasing number of studies have shown that natural products can fight colorectal cancer through the ROS pathway. Alantolactone is the main pharmacological component of the medicinal plant Inula helenium. In Ding's experiments, Alantolactone induced ROS overload in human SW480 and SW1116 colorectal cancer cells and led to extensive oxidative DNA damage and subsequent activation of the intrinsic apoptotic pathway to trigger cell death [23]. β-elemene is an active anti-cancer ingredient extracted from turmeric. Wang demonstrated that β-elemene inhibited the proliferation of colorectal cancer cells, induced cell cycle arrest in the G2/M phase, and increased ROS levels and promoted phosphorylation of AMPK protein in colorectal cancer cells [24]. Zhang demonstrated that oridonin caused caspase-dependent apoptosis and the suppression of proliferation in both 5-FU sensitive and resistant colorectal cancer (CRC) cells, induced ROS accumulation in them, and led to apoptosis. In contrast, oridonin-induced apoptosis was almost eliminated when cells were co-treated with the ROS scavenger N-acetyl-L-cysteine [25]. Sheikh's flow cytometry assay of citral revealed that citral induced activation of phosphatidylserine, decreased mitochondrial membrane potential in HCT116 and HT29 cells, increased intracellular ROS levels, and attenuated GSH levels in cells, which in turn led to apoptosis [26].

Lung cancer. Epidemiological statistics show that the incidence of lung cancer has grown faster in the last few years, and the prognosis of conventional chemotherapy is poor and survival rates are low, so the use of less toxic natural products could be a novel treatment. Wang's results of intracellular ROS components by fluorescent probe and flow cytometry showed that Alisol B-23-acetate induced an increase in intracellular ROS levels and significantly inhibited the proliferation of lung cancer cells in a dose-dependent manner [27]. Cucurbitacin B (CuB) can exert effective anti-tumor activity in lung cancer. Yuan reported that CuB directly binds to TLR4 to activate NLRP3 inflammatory vesicles, enhancing mitochondrial ROS production, calcium ion accumulation and release [28].

Liver cancer. Hepatocellular carcinoma is the most common form of liver cancer, and natural products have a significant impact on the development of liver cancer. In vitro experiments demonstrated that

Isoforretin A, a natural product of diterpenoids, significantly inhibited Trx1 activity, led to ROS accumulation and more extensive degradation of thiol redox homeostasis in cancer cells, causing death of hepatocellular carcinoma HepG2 cells [29]. Walsuronoid B enhances the production of hydrogen peroxide, nitric oxide, and superoxide anion radicals, resulting in elevated ROS levels. In addition, Walsuronoid B induced ROS to upregulate p53 levels, and ROS and p53 promoted each other and synergistically induced hepatocellular carcinoma cell death [30].

Cervical cancer. Cervical cancer is the most common gynecological tumor. In Zhang's study, santamarine mainly targets thioredoxin reductase and not only inhibits its recombination, but also inhibits cellular thioredoxin reductase activity, impairs its intracellular antioxidant function, and is accompanied by the accumulation of high levels of ROS in HeLa cells. Ultimately, this activity inducing oxidative stress-mediated apoptosis in tumor cells was shown to have a negative effect on the cell cycle [31]. Gong's findings demonstrate that the anti-tumor effects of rotundifuran may be related to the induction of mitochondria-dependent apoptosis by ROS through MAPK and PI3K/Akt signaling pathways [32].

Breast cancer. Breast cancer is one of the malignant tumors with high incidence and mortality rate in women worldwide. Terpenoids have received extensive attention in the field of anti-breast cancer research in the last few years due to their unique biological activities. Taicrypnacids induce a significant and dose-dependent increase in intracellular Ca^{2+} concentration and ROS levels, with vacuole-like morphological changes in the endoplasmic reticulum, which serves as a Ca^{2+} reservoir [33]. Liu reported the mechanism of JAK/STAT3 signaling regulation by parthenolide, a natural compound from the herb Pyrethrum parthenium that inhibited JAK/STAT3 signaling, induced ROS production, and suppressed IL-6-induced cancer cell migration [34].

Other cancers. Deoxyelephantopin (DET), the active ingredient in Elephantopus scaber, induces apoptosis in osteosarcoma cells by elevating ROS levels, dose-dependently decreasing the viability of osteosarcoma cells following elevated intracellular ROS levels, causing mitochondrial dysfunction and cysteine aspartase activation [35]. Dihydroartemisinin (DHA) has been shown to inhibit tumor growth, and Du in a further study found that DHA induced autophagy by modulating the activity of the AMPK/mTOR/p70S6k signaling pathway, accelerated the degradation of ferritin in leukemic cells, and promoted the accumulation of cellular ROS, ultimately leading to cellular scorching [36]. Genipin is the product of hydrolysis of gardenia glycosides by β-glucosidase, which has been reported to have significant anticancer effects. Cho presented an anti-cancer drug update on this compound, Genipin inhibits UCP2 to attenuate ROS production, leading to ROS/c-Jun N-terminal kinase-dependent apoptosis of cancer cells [37]. Triptolide, a natural product isolated from a traditional Chinese herb, was found by Cai to kill head and neck cancer cells by inducing Gasdermin E-mediated cell scorching and to inhibit the NRF2/SLC7A11 (also known as xCT) pathway and induce ROS accumulation [38].

Alkaloids

Alkaloids are nitrogen-containing alkaline organic compounds mainly found in plants. They were found to regulate the ROS level and exhibit high anti-tumor activity. Those natural products may inhibit cancer cell proliferation by affecting the cell division cycle.

Digestive system tumors. In a comparative study of the anticancer activity of berberine and GEM in pancreatic cancer, Park found that berberine induced apoptosis by inducing cell cycle arrest in the G1 phase, which elevated intracellular ROS and inhibited tumor growth in a dose-dependent manner [39]. In Zhang's study, sanguinarine upregulated miR-16 gene expression in hepatocellular carcinoma cells. Sanguinarine induced cell cycle arrest and ROS-associated apoptosis by significantly inhibiting HCC cell proliferation in a p53-dependent manner [40]. An's study revealed that Neferine has an anti-tumor proliferative effect in esophageal squamous cell carcinoma, causing intracellular accumulation of reactive oxygen species and activating the JNK pathway, which triggers cell cycle arrest in the G2/M phase and enhances apoptosis in esophageal squamous cell carcinoma cell lines [41].

Endocrine tumors. Piperlongumine is a natural alkaloid derived from long peppers, which selectively inhibits cancer cells by generating ROS. Kung observed activation of Erk and inhibition of the Akt/mTOR pathway via ROS induction in cells treated with piperlongumine, which mediates apoptosis of thyroid cancer cells via the ROS-Akt pathway [42].

Neurological tumors. Evodiamine is a major alkaloid isolated from Evodia rutaecarpa Bentham, with a variety of pharmacological activities. Liu found that evodiamine elevated ROS in glioblastoma cells and induced intracellular calcium/JNK signaling pathway autophagy and calcium/mitochondria-mediated apoptosis [43, 44].

Flavonoids

Flavonoids have a variety of biological activities, through anti-inflammatory, antioxidant and other ways to prevent and treat diseases, such as cardiovascular disease, diabetes, etc. In anti-cancer research, flavonoids have been shown to exert anti-cancer effects through various pathways, inhibiting the proliferation of tumor cells through various mechanisms such as inhibition of the NF-κB pathway in tumor cells, regulation of ROS levels, and causing cell cycle arrest.

Malignant mesotheliomas. Apigenin is a natural product mainly found in celery, and Lee's study showed that it significantly inhibited cell viability with a subsequent increase in intracellular ROS, leading to decreased mitochondrial membrane potential and ATP depletion, and suppressed the cell cycle in the G2/M phase. Therefore, this experiment suggests that apigenin can induce ROS-dependent cellular inflammatory death through mitochondrial dysfunction [45].

Hematologic tumors. Xanthohumol is an important natural product of hops, and in a study of human acute myeloid leukemia HL-60 cells, Wang detected xanthohumol-induced ROS production by flow cytometry, blocking the cell cycle in the G1 phase and inducing apoptosis in a dose-dependent manner [46].

Genitourinary tumors. Wu's results showed that gambogenic acid significantly promoted ROS production and endoplasmic reticulum stress. Gambogenic acid not only exhibited anti-proliferative and pro-apoptotic activities, but also participated in the induction of autophagy in PCa cells [47]. 3,5,7-Trihydroxyflavone (THF) inhibits the growth of a wide range of tumors, and a study reported the antiproliferative potential of THF in prostate cancer cell lines through a ROS-mediated cascade response. In the authors' mouse model, THF significantly inhibited tumor growth and increased mouse survival and ROS levels in esophageal adenocarcinoma cells [48].

Others. Quercetin induces transcription factor EB-mediated lysosomal activation and promotes lysosome-dependent ferritin degradation and free iron release, an effect synergistic with quercetin-induced ROS production, leading to lipid peroxidation and cellular scorching [49].

Phenolic

Most of the phenolic compounds present in nature are the result of plant life activities. The phenols contained in plants are called endogenous phenols, and the remaining are called exogenous phenols. Many studies have shown the potential for natural phenolic compounds in the prevention and treatment of tumors.

Head and neck tumors. Xiao and others conducted an experiment on the anti-tumor activity of 4-O-Methylhonokiol (MH) in human oral cancer cells, which observed the cytotoxicity of MH using methyl thiazolyl tetrazolium colorimetric assay, suggesting that MH may induce intracellular ROS production. The authors further calculated that intracellular ROS concentration increased dose-dependently [50]. Lin's experimental results indicate that Plumbagin induces apoptosis in drug-resistant oral cancer cells in vitro and in vivo by reducing tumor cell viability through ROS-mediated endoplasmic reticulum stress and mitochondrial dysfunction [51].

Digestive system tumors. The results obtained by Dando with cannabinoid-treated pancreatic cancer cells suggest that massive activation of AMPK is caused by a ROS-dependent increase in the

AMP/ATP ratio. These cellular physiological changes induced by cannabinoids inhibit pancreatic cancer cell growth and induce cellular autophagy [52]. Erianin inhibits the growth and metastasis of colorectal cancer cells by inducing iron death and elevating the concentration of ROS [53].

Osteosarcoma. A study found that erianin, a natural product derived from the orchid Dendrobium, inhibited cell viability of osteosarcoma cells, increased ROS levels via the ROS/JNK signaling pathway, and induced G2/M phase arrest and cellular autophagy [54].

Breast cancer. Phytochemical carnosol, extracted from rosemary, is a natural polyphenolic compound with strong anti-triple-negative breast cancer effects, which exhibits significant anti-tumor effects by elevating ROS levels and activating the ROS-dependent MAPK pathway to induce apoptosis [55].

Esters

In recent years, esters of natural origin have been shown to induce anti-tumor effects by increasing the level of ROS due to their good biological activity and medicinal value.

Breast cancer. The natural small molecule withangulatin A (WA) is present in narrowly folate plasma, and affinity protein analysis has shown that WA can bind directly to covalent phosphoglycerate dehydrogenase and inactivate its enzymatic activity. By inhibiting WA-mediated phosphoglycerate dehydrogenase, glutathione synthesis is reduced and intracellular ROS levels are increased, thereby inhibiting tumor proliferation [56]. Myricanol-9-acetate was isolated and purified from the ethyl acetate extract of poplar. In breast cancer MCF-7 cells treated with different concentrations of Myricanol-9-acetate, Ahmad showed an increased expression of cleaved caspase-3, cleaved PARP and Bax, decreased the expression of Bcl-2, generated large amount of ROS, and cell proliferation was inhibited [57].

Digestive system tumors. Levistolide A is a natural compound isolated from the traditional Chinese herb Chuanxiong, and Yang found in a study of HCT116 and its homologue p53-/-colon cancer cells that levistolide A induced apoptosis in colon cancer cells via the ROS-mediated ER stress pathway [58]. A study investigated the in vitro and in vivo effects of Xanthatin on pancreatic cancer and its molecular mechanisms. Xanthatin prevented the proliferation and metastasis of pancreatic cancer cells and triggered phosphatidylserine exposure, chromatin condensation, and cysteinyl asparaginase activation, which significantly up-regulated the level of ROS in pancreatic cancer cells, thereby inducing apoptosis [59].

Respiratory tumors. Patrycja validated the anticancer properties of resveratrol ester derivatives in order to expand the use of resveratrol and enhance its activity. The derivatives also increased apoptosis of tumor cells by altering the cysteine asparaginase activity of the pro-apoptotic pathways (p21, p53 and Bax), elevating the level of ROS and at the same time decreasing the tolerance of tumor cells to high levels of ROS [60].

Polysaccharide

Recent studies revealed that polysaccharide compounds have a variety of pharmacological activities such as immunomodulatory, anti-tumor, antiviral, hypoglycemic, etc. Their anti-tumor activity has received the most attention from researchers, who have shown that they exert anti-tumor effects by upregulating the level of ROS.

In Goutouzao's study, Liang showed that it enhanced the viability of mouse mononuclear macrophages cells, activated the immune response, and increased intracellular ROS to induce apoptosis in colorectal cancer cells [61]. Lentinan is a potent active ingredient extracted from high-quality shiitake mushroom seeds. In the study of Li, the mechanism of anti-inflammatory function of Lentinan in lung cancer cells was investigated. Lentinan decreased inflammatory cytokines IL-6 and IL-1 in LPS-stimulated A549 cells, altering the oxidative state of the cells by increasing intracellular ROS content and attenuating the activity of GPx4 [62].

Other compounds

The inhibitory effect of curcumin on glioblastoma was dose-dependent and the detection of ROS using the fluorescent molecular probe CMH2DCFA indicated that curcumin-treated cells induced an elevation of ROS, which was reversed if the antioxidant N-acetylcysteine was pretreated [63]. The coumarin derivative Fraxetin (7,8-dihydroxy-6-methoxycoumarin) has antioxidant, anti-inflammatory and neuroprotective effects, and Kundu found that it promotes ROS production, induces phosphorylation of AMP-activated protein kinase alpha and inhibits tumor cell growth in a concentration-dependent manner [64]. Amir R. and others used Auraptene to treat U87 cells and found that the ROS concentration showed a decrease followed by an increase with time. The auraptene-induced cytotoxicity is triggered through ROS production, upregulation of Bax/Bcl-2 ratio and regulation of cell cycle-related gene expression that leads to apoptosis [65]. In an in vitro study, Hussain and others reported that thymoquinone, a natural compound isolated from Nigella sativa, was responsible for the release of ROS in B-cell lymphoma cells, and inhibited the activity of NF-κB. This leads to inhibition of cell viability and induction of mitochondria-dependent apoptosis in diffuse large B-cell lymphoma cell lines [66].Chaetocin is a diketopiperazine compound derived from the fungus Trichoderma spp. In a melanoma study, the results obtained after treatment with different concentrations of chitin and different durations indicated that chitin significantly elevated ROS levels of cells in a time- and concentration- dependent manner and played an important role in the induction of apoptosis [67] (Table 1).

Due to the lack of mechanoselectivity of most natural compounds, natural products showed multiple effects in different cancers [68, 69]. Combined with the literature we searched, it is known that in a variety of tumors such as colon cancer, pancreatic cancer, liver cancer, lung cancer, breast cancer, etc., are more sensitive to the ROS produced by natural products. The elevated ROS induces tumor cell apoptosis further [70, 71]. It is known that natural products such as terpenoids, alkaloids, flavonoids, phenols, esters, etc., which have a wide range of basic research, are prone to produce ROS and exert anti-tumor activity through the ROS pathway.

Adjunctive role of natural products in anti-tumor therapy

Although numerous studies have clearly shown that natural products can exert anti-tumor effects through modulation of ROS, most of these studies have focused on cellular experiments and animal studies. Including some of the newly developed anti-tumor herbal medicines, there are few studies indicating the use of a compound alone in the clinical setting in the absence of traditional chemotherapy to treat tumors. Most of them are based on first-line chemotherapeutic drugs which mechanistically serve to enhance the killing effect of chemotherapeutic drugs on tumor cells or reduce the toxic side effects of chemotherapeutic drugs through ROS or other related signaling pathways, so as to compensate for the limitations of chemotherapeutic drugs and improve the anti-tumor effect (Figure 3).

Drugs that act on the chemical structure of DNA

Cytotoxic chemotherapeutic agents such as cisplatin and oxaliplatin can directly bind to DNA, thereby destroying its structure and function.

Cisplatin. Cisplatin has been reported to induce nephrotoxicity through direct induction of inflammatory responses and oxidative stress, whereas histological changes in the kidney were significantly attenuated by xanthohumol intervention, with reduced production of serum creatinine and urea nitrogen and suppressed changes in malondialdehyde and ROS levels [72]. Therefore, xanthohumol prevents cisplatin-induced nephrotoxicity by ameliorating inflammatory and oxidative responses [73]. β-elemene can increase intracellular ROS levels and has potential therapeutic applications in colorectal cancer [24]. β-elemene was found to enhance cisplatin-induced apoptosis in bladder cancer cells through the ROS-AMPK signaling pathway, and the combination with cisplatin enhanced cytotoxicity [74]. Auraptene treatment of malignant glioma

Table 1 Natural compounds with anti-tumor effect by increasing ROS

Category	Nature product	Source species	Cancer type	Target cell lines	Pathway	Time/dose dependence	Cell cycle block	Reference
Terpenoids	alantolactone (ATL)	*Inula helenium*	Colon cancer	SW480 & SW1116 Colorectal cancer cells	/	/	G1	[23]
	β-elemene	turmeric	Colon cancer	MDA-MB-231 cells	ROS/AMPK/mTOR pathway	/	G2/M	[24]
	oridonin	*Rabdosia rubescens*	/	CRC cells	ROS/JNK/c-Jun pathway	/	/	[25]
	citral	Plants with lemon scent	/	HCT116 & HT29 cells	p53/ROS pathway	/	/	[26]
	Alisol B-23-acetate	*Alisma orientale*	Lung cancer	A549 & NCI-H292 cells	Mitochondrial pathway	Dose-dependent	/	[27]
	Cucurbitacin B（CuB）	muskmelon pedicel	Lung cancer	NSCLC cells	TLR4/NLRP3/GSDMD	/	/	[28]
	Isoforretin A	*Isodon forrestii*	Liver cancer	HepG2 cells	Inhibit Trx1	/	/	[29]
	Walsuronoid B	Stems and leaves of red beans	Liver cancer	HepG2 & Bel-7402 cells	p53/ROS pathway	/	G2/M	[30]
	Santamarine	*Ambrosia confertiflora*	Cervical cancer	HeLa cells	Target TrxR	/	/	[31]
	Rotundifuran	*Vitex trifolia*	Cervical cancer	HeLa & SiHa cells	MAPK & PI3K/Akt pathway	/	/	[32]
	Taicrypnacids	*Taiwania cryptomerioides*	/	MCF-7 & HCT-116 cells	Ca^{2+}/ROS pathway	Dose-dependent	/	[33]
	Parthenolide	Feverfew	/	HEK293 cells	Inhibit JAK/STAT3 signal transduction	/	/	[34]
	Deoxyelephantopin	*Elephantopus scaber*	Osteosarcoma	Osteosarcoma cells	Inhibit NF-κB activation	Dose-dependent	/	[35]
	Dihydroartemisinin	*Artemisia annua*	Leukemia	AML cells	AMPK/mTOR/p70S6k pathway	/	G0/G1	[36]
	Genipin	*Gardenia jasminoides*	/	/	ROS/JNK/c-Jun pathway	/	/	[37]
	triptolide	*Tripterygium wilfordii* Hook f	Head & neck cancer	Head and neck cancer cells	Inhibit NRF2 / SLC7A11 pathway	/	/	[38]
Alkaloids	Berberine	berberis	Pancreatic cancer	PANC-1 & MIA-PaCa2 cells	/	Dose-dependent	G1	[39]
	Sanguinarine	*Sanguinaria canadensis*	Liver cancer	HCC cells	p53/ROS pathway	/	/	[40]
	Neferine	*Nelumbo nucifera*	Esophageal Cancer	ESCC cells	ROS/JNK/c-Jun pathway	/	G2/M	[41]
	Piperlongumine	long pepper	Thyroid cancer	TC cell lines	Inhibit Akt/mTOR pathway	Time & dose-dependent	/	[42]
	Evodiamine	*Evodia rutaecarpa Bentham*	Glioblastoma	Glioblastoma cells	Ca^{2+}/JNK pathway	/	G2/M	[41, 42]
	Apigenin	Celery	Malignant mesothelioma	MSTO-211H & H2452 cells	/	/	G2/M	[45]
	Xanthohumol	*Humulus lupulus*	Acute myeloid leukemia	HL-60 cells	/	Dose-dependent	G1 phase	[46]
	Quercetin	Multiple plants	/	Various cancer cell lines	transcription factor EB-ROS mediates	/	/	[49]
	Gambogenic acid	Gamboge	Prostate cancer	PC3 and DU145 cells	JNK pathway	Dose-dependent	/	[47]
	3,5,7-trihydroxyflavone	/	Prostate cancer	EAC cells	Mitochondria-mediated apoptosis	Time & dose-dependent	G2/M	[48]
Phenolic	4-O-Methylhonokiol	*Magnolia officinalis*	Oral cancer	OSCC PE/CA-PJ41 cells	/	Dose-dependent	G2/M	[50]

Table 1 Natural compounds with anti-tumor effect by increasing ROS (*continued*)

Category	Nature product	Source species	Cancer type	Target cell lines	Pathway	Time/dose dependence	Cell cycle block	Reference
	Cannabinoids	Cannabis	Pancreatic cancer	Panc1 cells	Akt/c-Myc pathway	/	/	[52]
	Erianin	Dendrobium	Osteosarcoma	Osteosarcoma cells	ROS/JNK pathway	/	G2/M	[54]
	phytochemical carnosol	Rosemary	Triple-negative breast cancer	MDA-MB-72 cells	MAPK pathway	Dose-dependent	G2	[55]
	Erianin	Honeysuckle	Colorectal cancer	CRC cells	Ras/Raf/MEK/MAPK-ERK pathway	Dose-dependent	/	[53]
	Plumbagin	*Plumbago zeylanica* L	Oral cancer	CR-SAS cells	endoplasmic reticulum stress pathway	/	/	[51]
Esters	withangulatin A	*Physalis angulata*	/	ZR-75-1, HCT-116 &	Induces PHGDH inactivation	/	/	[56]
	Myricanol-9-acetate	Myricanol	/	MCF-7 breast cancer cells	/	Dose-dependent	G0/G1	[57]
	Levistolide A	*Ligusticum chuanxiong Hort*	Colon cancer	HCT116 cells	ROS-mediated ER stress pathway	/	/	[58]
	resveratrol derivatives	Resveratrol	Lung cancer	A549 cells and HT29 cells	pro-apoptotic pathways (p21, p53, and Bax)	Dose-dependent	/	[60]
	Xanthatin	*Xanthium strumarium* L	Pancreatic cancer	BxPC-3 and PANC-1 cells	ROS/RBL1 signal pathway	Dose-dependent	/	[59]
Polysaccharide	Goutouzao	*Ziziphus jujube*	Colorectal cancer	LoVo cells	Activating the immune response	/	G0/G1	[61]
Polysaccharide	Lentinan	*Lentinula edodes*	Lung cancer	A549 cells	/	/	/	[62]
Diketones	Curcumin	Turmeric	Glioblastoma	Glioblastoma stem cells	MAPK pathway	Dose-dependent	/	[63]
Coumarins	Fraxetin	*Fraxinus bungeana A.DC.*	/	HaCaT cells	Akt/Nrf2 pathway	Dose-dependent	/	[64]
Diketopiperazines	chaetocin	fungi	Melanoma	Sk-Mel-28 & A375 cells	Mitochondrial pathway	Time & dose-dependent	/	[65]
/	Auraptene	Citrus	Malignant glioma	U87 cells	/	Dose-dependent	/	[66]
Phytochemicals	Thymoquinone	*Nigella sativa*	Lymphoma	ABC-DLBCL cell lines	Inhibit NF-κB activation	/	/	[67]

ROS, reactive oxygen species.

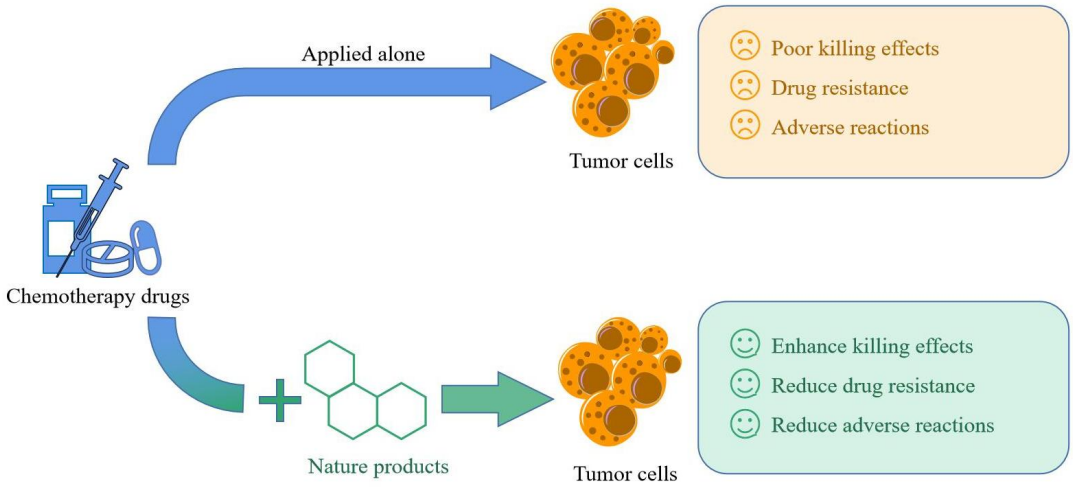

Figure 3 Advantages of chemotherapy drugs combined with natural products against tumors. Chemotherapeutic drugs applied alone in anti-tumor therapy often encounter disadvantages such as poor killing effect on tumor cells, causing resistance of tumor cells, and more adverse reactions. When chemotherapeutic drugs are combined with natural products for antitumor treatment, natural products can play a role in reducing the occurrence of adverse reactions, decreasing the resistance of tumor cells to chemotherapeutic drugs, and enhancing the killing effect of chemotherapeutic drugs on tumor cells. The introduction of natural products plays a very good adjuvant effect.

U87 cells has been demonstrated to induce ROS production and exert cytotoxic effects [65]. Moussavi performed a series of experiments on colon cancer cells, in which the combination of Auraptene + cisplatin treatment of HT29 cells resulted in a significantly stronger inhibitory effect than cisplatin treatment alone [75]. CuB is a natural product with anti-tumor activity against a variety of cancer cell lines [28]. The combination treatment of cisplatin-resistant cell lines with CuB + cisplatin by El-Senduny resulted in decreased Dyrk1B kinase levels, increased ROS, decreased pERK1/2 and pSTAT3 levels, and significantly increased the cytotoxicity of cisplatin [76]. DHA inhibits the proliferation of myeloid leukemia cells via the ROS pathway, and Du found that it enhances the cytotoxicity of cisplatin, and the combination of the two inhibits the proliferation of pancreatic cancer cells and induces DNA damage, exerting a synergistic anti-tumor effect [36, 77].

Oxaliplatin. Alantolactone induction of ROS has been identified in studies of colorectal cancer, It activated JNK and p38 MAPK signaling pathways and enhanced oxaliplatin-induced growth inhibition and apoptosis in HCT116 and RKO cells [23]. Compared with monotherapy, combination therapy showed higher anti-tumor activity [78]. Kim's in vivo and in vitro studies on genipin showed that the combination with oxaliplatin exerts synergistic anti-tumor effects via the ROS/endoplasmic reticulum stress/BIM pathway in colorectal cancer cell lines [79]. Both the current reported studies on erianin inhibition in bladder cancer and osteosarcoma exert their anti-tumor effects through the ROS pathway, it significantly inhibited the proliferation of human colon cancer oxaliplatin-resistant cells and suppressed the cell cycle in the G2/M phase, indicating that erianin modulates the multi-drug resistance phenotype of oxaliplatin-resistant cells [54, 80, 81]. In Chen's colorectal cancer study, a combination regimen containing oxaliplatin and piperlongumine was used and intracellular oxidative stress effects accompanied by elevated ROS were detected. The author demonstrated that oxaliplatin increased ROS levels and showed a synergistic anticancer effect with piperlongumine in cancer cells [82].

Drugs that affect nucleic acid synthesis

Drugs that affect nucleic acid synthesis, also known as antimetabolites, inhibit dividing and reproducing by specifically interfering with the metabolism of nucleic acids. For example, GEM and 5-FU inhibit DNA polymutase and thymidine nucleoside synthase, respectively. As mentioned earlier, DET exerts its anti-osteosarcoma effect mediated by elevating ROS, Ji's experiments showed that DET enhanced the sensitivity of GEM by inhibiting the NF-κB signaling pathway, which not only inhibited the growth and metastasis of pancreatic tumors, but also enhanced the anti-tumor capacity of GEM [35, 83]. Yang showed that combination of GEM and triptolide was more cytotoxic than alone, and that the combination induced cell cycle arrest in the G1 phase and elevated ROS [84]. Piperlongumine has been shown to inhibit thyroid cancer via the ROS pathway, and in combination experiments with GEM, it exerts a synergistic effect against KRAS-mutated lung cancer, inducing apoptosis and increasing ROS content and LC3B-II expression [42, 85]. 5-FU improves the clinical prognosis of colorectal cancer but is prone to NNMT-induced resistance. Recent studies have demonstrated that curcumin reverses this resistance by increasing ROS and cell cycle arrest in colorectal cancer cells, thereby enhancing the anti-tumor activity of 5-FU [86].

Drugs that act on nucleic acid transcription

Drugs such as adriamycin, epirubicin and pirarubicin selectively act on the DNA template and inhibit DNA-dependent RNA polymerase, thereby inhibiting RNA synthesis. Hydrotyrosol is able to counteract adriamycin-induced cytotoxicity in cardiomyocytes by acting on SOD2 levels and oxidative responses and apoptotic mechanisms mediated by Bcl-2/Bax, and does not interfere with the anti-tumor properties of adriamycin in osteosarcoma cells [87]. Increased MX2 cell death was observed after co-treatment with genipin and different doses of menadione, adriamycin and epirubicin, which was also accompanied by an increase in cellular ROS levels, enhancing the sensitivity of drug-resistant cancer cells to cytotoxic drugs [88]. In the experiments, oridonin was shown to enhance the anti-tumor effect of adriamycin in human osteosarcoma cells in the presence of its subcytotoxic concentration in combination with adriamycin [89]. Thymoquinone exerts anti-tumor effects in kidney cancer and lymphoma through a ROS-dependent mechanism [65, 90]. In studies of adult T-cell leukemia, the combination of the two had a greater ability to inhibit cellular activity than did thymoquinone or adriamycin alone, and the combination induced apoptosis by increasing ROS and causing disruption of the mitochondrial membrane potential [91]. Awasthee found that piperlongumine enhances the efficacy of adriamycin in breast cancer and is involved in the regulation of glucose, elevation of ROS and regulation of IncRNA expression [92].

Drugs that interfere with microtubule protein synthesis

Some drugs, such as paclitaxel and docetaxel, which affect microtubule protein assembly, interfere with spindle formation in mitosis, causing cell stop at mid-division. The effects of ROS modulation on apigenin in particular may be shown to exert an anti-malignant glioma effect, it also sensitized cancer cells to paclitaxel-induced apoptosis by inhibiting SOD activity, which led to accumulation of ROS and cleavage of cystein-2, suggesting that the combination of apigenin and paclitaxel could exert synergistic anti-tumor effects and reduce the dose of paclitaxel [45, 93]. The anti-tumor effect of Lentinan via ROS has been demonstrated, while co-treatment with paclitaxel and Lentinan further triggered ROS production and increased thioredoxin-interacting protein expression, and the combination of both had a significantly stronger inhibitory effect on A549 cell proliferation than treatment with paclitaxel alone [62, 94]. Qu's study found that CuB reduced the resistance of ovarian cancer cells to paclitaxel and enhanced the anti-tumor activity of paclitaxel [95]. Quercetin promotes p53 non-dependent cell death in various cancer cell lines [49]. A trial showed that combined treatment with quercetin and paclitaxel significantly inhibited cell proliferation, increased apoptosis, blocked the cell cycle in the G2/M phase, inhibited cell migration, and increased ROS production [96]. The upregulation of intracellular ROS by piperlongumine synergizes with paclitaxel in human intestinal cancer cells, enhancing its anti-tumor effects [97].

Topoisomerase I inhibitor

Irinotecan inhibits topoisomerase I directly, which inhibits DNA replication and RNA synthesis. Lei conducted in vivo and in vitro experiments on irinotecan and its metabolite SN-38, respectively, and showed that the anti-tumor effect of quercetin in combination with irinotecan was superior to that of high-dose irinotecan alone. Thus, quercetin in combination with irinotecan is shown to enhance its anti-tumor activity [98]. Curcumin can induce apoptosis and inhibit cell proliferation through the ROS pathway. Curcumin has been reported to synergize with a variety of chemotherapeutic agents, such as irinotecan, adriamycin, and docetaxel, to inhibit their growth in different types of tumor cells [99].

Monoclonal antibodies

Cetuximab has the ability to kill tumor cells or inhibit tumor cell proliferation through a high degree of receptor selectivity via antibody-dependent cytotoxic effects.β-elemene promotes intracellular ROS production. In KRAS mutant CRC cells, Chen found that combination treatment with β-elemene and cetuximab can occur to induce cell scorching and inhibit epithelial mesenchymal transition, which play a synergistic role in anti-CRC [100]. Oridonin in combination with cetuximab inhibits laryngeal squamous cell carcinoma by synergistic action, inducing ROS production after 1.5 h of application, followed by G2/M phase arrest and apoptosis [101].

Other types of drugs

Arsenic analogs have achieved remarkable success in the treatment of patients with acute promyelocytic leukemia and when applied with β-elemene in a multidrug combination strategy, synergistic anti-tumor

effects can be achieved [102]. Acquired oxitinib resistance is encountered in the treatment of EGFR-mutant non-small cell lung cancer, but DHA can reverse this resistance by increasing ROS levels and reducing heme metabolism [103]. A prospective study on thyroid cancer to determine the effect of the combination of evodiamine and belestat (PXD101) showed that the combination induced apoptosis by inhibiting PI3K/Akt signaling and increasing ROS levels, which exerted a synergistic anti-cancer effect [104] (Table 2).

In addition to basic studies, some clinical studies demonstrated that natural products exert better anti-tumor effects in combination with chemotherapeutic drugs through ROS pathway. Genistein is an estrogen-like isoflavone compound found in legumes. As a structural analog of genistein, phenoxydiol has broad-spectrum anti-tumor activity [105]. A phase II clinical trial of phenoxodiol in combination with commonly used chemotherapeutic agents showed that the compound increased the level of ROS in tumor cells, improved their sensitivity to chemotherapeutic agents, and reversed the resistance of cisplatin and paclitaxel [105].

Discussion and conclusion

In this review, we have systematically summarized the recent studies related to the anti-tumor active ingredients in natural compounds in terms of elevating ROS levels. It is not difficult to find that these studies involve various tumor diseases, from a variety of different signaling pathways such as Wnt/β-catenin pathway, p38/MAPK pathway, ROS/JNK pathway, AKT pathway, etc. to elevate intracellular ROS levels to enhance intracellular oxidative stress, induce cell cycle arrest, induce apoptosis and finally achieve the purpose of anti-tumor.

Due to the paucity of current clinical studies on natural products, it is difficult for this review to provide a detailed discussion on specific clinical doses and other aspects of use, thus it is difficult to serve as a direct guide to clinical application. Therefore, it is necessary to understand clearly the position of natural products in anti-tumor and not overestimate or ignore its role. It is noteworthy that the present marketed anti-tumor herbal medicines have emerged from related studies. Rhubarb is one of the compounding ingredients used in Ganfule tablets. The active ingredient rhein has anti-tumor activity, and the combination therapy with oxaliplatin synergistically enhances pancreatic cancer cell apoptosis by increasing intracellular ROS production and PI3K/AKT pathway inactivation [106]. Ankangxin Capsules contain ganoderma lucidum, and its active ingredient ganoderic acid D can enhance the therapeutic effect of cisplatin on SKOV3 and cisplatin-resistant SKOV3/DDP cells by increasing intracellular ROS [107]. This theory can be built upon and gradually explored in clinical trials, while ensuring the safety and effectiveness of conventional chemotherapy, so as to find the best combination between natural products and conventional chemotherapeutic agents.

In addition to the above, affecting the tumor microenvironment is an important means of eliminating tumor cells. Cellular homeostatic mechanisms, including calcium ion homeostasis in vivo, protein homeostasis, and redox homeostasis help maintain internal stability in response to environmental perturbations. ROS is key to the anti-cancer effects of natural products, and increasing ROS level disrupt the initial redox homeostasis within tumor cells. The tumor microenvironment is necessary for the survival and development of tumor cells, and immune activation is an important means of eliminating tumor cells

Table 2 Adjunctive role of natural products in anti-tumor therapy

Nature product	Chemotherapy drugs	Combination effect	Tumor type	Reference
Apigenin	Paclitaxel	Synergistic anti-tumor	Cervical cancer	[93]
Deoxyelephantopin	Gemcitabine	Synergistic anti-tumor	Pancreatic cancer	[83]
Alantolactone	Oxaliplatin	Synergistic anti-tumor	Colon cancer	[78]
Lentinan	Paclitaxel	Synergistic anti-tumor	Lung cancer	[94]
Xanthohumol	Cisplatin	Reduction of nephrotoxicity	/	[73]
β-elemene	Cetuximab	Synergistic anti-tumor	Colorectal cancer	[100]
	Cisplatin	Synergistic anti-tumor	Bladder cancer	[74]
	Arsenic-based drugs	Synergistic anti-tumor	Solid tumor	[102]
Auraptene	Cisplatin	Synergistic anti-tumor	Colon adenocarcinoma	[75]
Cucurbitacin B	Cisplatin	Synergistic anti-tumor	Ovarian cancer	[76]
	Paclitaxel	Reducing drug resistance	Ovarian carcinoma	[95]
Curcumin	5-FU	Reducing drug resistance	Colorectal cancer	[86]
	Adriamycin	Synergistic anti-tumor	Colon cancer	[99]
	Cisplatin	Synergistic anti-tumor	Liver cancer	[99]
	Docetaxel	Synergistic anti-tumor	Breast cancer	[99]
Dihydroartemisinin	Cisplatin	Synergistic anti-tumor	Pancreatic cancer	[77]
	Ocetinib	Reducing drug resistance	Lung cancer	[103]
Hydroxytyrosol	Adriamycin	Reduces cardiotoxicity	Osteosarcoma	[87]
Genipin	Oxaliplatin	Synergistic anti-tumor	Colorectal cancer	[79]
	Menaquinone	Reducing drug resistance	Leukemia	[88]
	Adriamycin	Reducing drug resistance	Leukemia	[88]
	Epirubicin	Reducing drug resistance	Leukemia	[88]
Erianin	Oxaliplatin	Reducing drug resistance	Colon cancer	[81]
Evodiamine	Belinostat	Synergistic anti-tumor	Thyroid carcinoma	[104]
Triptolide	Gemcitabine	Synergistic anti-tumor	Bladder cancer	[84]
Oridonin	Cetuximab	Synergistic anti-tumor	Laryngeal cancer	[101]
	Adriamycin	Synergistic anti-tumor	Osteosarcoma	[89]
Thymoquinone	Adriamycin	Synergistic anti-tumor	Leukemia	[91]
Quercetin	Irinotecan	Synergistic anti-tumor	Gastric cancer	[98]
	Paclitaxel	Synergistic anti-tumor	Prostate cancer	[96]
Piperlongumine	Paclitaxel	Synergistic anti-tumor	Intestinal cancer	[97]
	Gemcitabine	Synergistic anti-tumor	Lung cancer	[85]
	Oxaliplatin	Synergistic anti-tumor	Colorectal cancer	[82]
	Adriamycin	Synergistic anti-tumor	Breast cancer	[92]

by remodeling the tumor microenvironment [108]. It has been found that various natural products can target and regulate immune cells in the tumor microenvironment, such as T cells, macrophages, mast cells, and inflammatory cytokines. Natural products elevate the level of ROS, and disrupted the homeostatic balance of the tumor microenvironment, then activated the immune response through various mechanisms, with incalculable potential for tumor immunotherapy [109].

Iron, as an important trace element, plays a key role in biological processes such as cell proliferation, metabolism and mitochondrial function. However, disruption of iron homeostasis predisposes to cell death and various diseases because it acts as a mediator to promote ROS production [110]. ROS plays a crucial role in cell death processes including apoptosis, autophagy, and iron death. ROS is involved in the oxidation of lipids and the generation of lipid ROS, lipid peroxyl radicals, and other compounds associated with them, then exert cytotoxicity through the destruction of a wide range of biomolecules [111].

In the exploration of clinical trials, there are various difficulties and challenges. As a reason for the absence of more clinical studies on natural compounds, I consider several aspects to be relevant: (1) Unsatisfactory therapeutic effects of certain natural products due to low bio-availability in the body or lack of efficacy. (2) Certain natural compounds exhibit difficult physical and chemical properties to extract and separate, or their deficiency of stability renders them difficult to store and transport. (3) The in vivo toxic effects were not elucidated and no corresponding antidote for poisoning was found. (4) Potential drug interactions may occur, etc.

To address these critical issues, several breakthroughs have been made in recent years, such as enabling nanoparticles to act as drug carriers and loading different drugs into co-delivery systems. Arsenic-based drugs can be applied to acute promyelocytic leukemia, but application to solid tumors is difficult because of the contradiction between therapeutic efficacy and systemic toxicity. Liu and others synthesized biocompatible polyethyleneglycolated arsenic nanodots that can selectively and effectively treat solid tumors, and polyethyleneglycolated arsenic nanodots achieved a multi-drug combination strategy when applied with β-elemene for synergistic anti-tumor effects [102]. Pang co-loads precursors of both CuB and paclitaxel into pericentriolar material micelles and once it enters cancer cells, pericentriolar material releases CuB and paclitaxel in response to ROS [112].

These experimental studies not only improve the bioavailability and stability of natural products, but also avoid anachronistic interactions between drugs, which largely make up for the current shortcomings and can serve as a new idea for natural products to play an adjuvant therapeutic role and provide strong theoretical support for future clinical studies.

In conclusion, changes in ROS levels play an important role in the synergistic anti-tumor use of natural products as adjuvants to conventional chemotherapeutic agents. A large number of clinical studies is also needed to support the evidence, in order to seek better treatment options and to play a clinical guidance role for oncology patients.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA A Cancer J Clin* 2021;71(3):209–249. Available at: http://doi.org/10.3322/caac.21660
2. Wang K, Chen Q, Shao Y, et al. Anticancer activities of TCM and their active components against tumor metastasis. *Biomed Pharmacother* 2021;133:111044. Available at: http://doi.org/10.1016/j.biopha.2020.111044
3. DeNicola GM, Karreth FA, Humpton TJ, et al. Oncogene-induced Nrf2 transcription promotes ROS detoxification and tumorigenesis. *Nature* 2011;475(7354):106–109. Available at: http://doi.org/10.1038/nature10189
4. Lee HY, Nga HT, Tian J, Yi HS. Mitochondrial Metabolic Signatures in Hepatocellular Carcinoma. *Cells* 2021;10(8):1901. Available at: http://doi.org/10.3390/cells10081901
5. Yang C, Wu S, Mou Z, et al. Exosome-derived circTRPS1 promotes malignant phenotype and CD8+ T cell exhaustion in bladder cancer microenvironments. *Mol Ther* 2022;30(3):1054–1070. Available at: http://doi.org/10.1016/j.ymthe.2022.01.022
6. Yang Y, Karakhanova S, Hartwig W, et al. Mitochondria and Mitochondrial ROS in Cancer: Novel Targets for Anticancer Therapy. *J Cell Physiol* 2016;231(12):2570–2581. Available at: http://doi.org/10.1002/jcp.25349
7. Qian Q, Chen W, Cao Y, et al. Targeting Reactive Oxygen Species in Cancer via Chinese Herbal Medicine. *Oxid Med Cell Longev* 2019;2019:9240426. Available at: http://doi.org/10.1155/2019/9240426
8. Gaikwad S, Srivastava SK. Role of Phytochemicals in Perturbation of Redox Homeostasis in Cancer. *Antioxidants* (*Basel*) 2021;10(1):83. Available at: http://doi.org/10.3390/antiox10010083
9. Dong S, Guo X, Han F, He Z, Wang Y. Emerging role of natural products in cancer immunotherapy. *Acta Pharm Sin B* 2022;12(3):1163–1185. Available at: http://doi.org/10.1016/j.apsb.2021.08.020
10. NavaneethaKrishnan S, Rosales JL, Lee KY. ROS-Mediated Cancer Cell Killing through Dietary Phytochemicals. *Oxid Med Cell Longev* 2019;2019:9051542. Available at: http://doi.org/10.1155/2019/9051542
11. Park MN, Song HS, Kim M, et al. Review of Natural Product-Derived Compounds as Potent Antiglioblastoma Drugs. *Biomed Res Int* 2017;2017:8139848. Available at: http://doi.org/10.1155/2017/8139848
12. Kumari S, Badana AK, G MM, G S, Malla R. Reactive Oxygen Species: A Key Constituent in Cancer Survival. *Biomark Insights* 2018;13:117727191875539. Available at: http://doi.org/10.1177/1177271918755391
13. Sies H, Jones DP. Reactive oxygen species (ROS) as pleiotropic physiological signalling agents. *Nat Rev Mol Cell Biol* 2020;21(7):363–383. Available at: http://doi.org/10.1038/s41580-020-0230-3
14. Moloney JN, Cotter TG. ROS signalling in the biology of cancer. *Semin Cell Dev Biol* 2018;80:50–64. Available at: http://doi.org/10.1016/j.semcdb.2017.05.023
15. Minz AP, Das B, Mohapatra D, Suresh V, Mishra S, Senapati S. Gemcitabine induces polarization of mouse peritoneal macrophages towards M1-like and confers antitumor property by inducing ROS production. *Clin Exp Metastasis* 2022;39(5):783–800. Available at: http://doi.org/10.1007/s10585-022-10178-3
16. Mirzaei S, Hushmandi K, Zabolian A, et al. Elucidating Role of Reactive Oxygen Species (ROS) in Cisplatin Chemotherapy: A Focus on Molecular Pathways and Possible Therapeutic Strategies. *Molecules* 2021;26(8):2382. Available at: http://doi.org/10.3390/molecules26082382
17. Li B, Zhou P, Xu K, et al. Metformin induces cell cycle arrest, apoptosis and autophagy through ROS/JNK signaling pathway in human osteosarcoma. *Int J Biol Sci* 2020;16(1):74–84. Available at: http://doi.org/10.7150/ijbs.33787
18. Sznarkowska A, Kostecka A, Meller K, Bielawski KP. Inhibition of cancer antioxidant defense by natural compounds. *Oncotarget* 2016;8(9):15996–16016. Available at: http://doi.org/10.18632/oncotarget.13723
19. Wang N, Wu Y, Bian J, et al. Current Development of ROS-Modulating Agents as Novel Antitumor Therapy. *Curr Cancer Drug Targets* 2017;17(2):122–136. Available at:

http://doi.org/10.2174/1568009616666160216125833
20. Zhang S, Liu Q, Chang M, et al. Chemotherapy impairs ovarian function through excessive ROS-induced ferroptosis. *Cell Death Dis* 2023;14(5):340. Available at: http://doi.org/10.1038/s41419-023-05859-0
21. Samandari Bahraseman MR, Khorsand B, Zareei S, Amanlou M, Rostamabadi H. Various concentrations of hesperetin induce different types of programmed cell death in human breast cancerous and normal cell lines in a ROS-dependent manner. *Chem Biol Interact* 2023;382:110642. Available at: http://doi.org/10.1016/j.cbi.2023.110642
22. Abu Izneid T, Rauf A, Shariati MA, et al. Sesquiterpenes and their derivatives-natural anticancer compounds: An update. *Pharmacol Res* 2020;161:105165. Available at: http://doi.org/10.1016/j.phrs.2020.105165
23. Ding Y, Wang H, Niu J, et al. Induction of ROS Overload by Alantolactone Prompts Oxidative DNA Damage and Apoptosis in Colorectal Cancer Cells. *Int J Mol Sci* 2016;17(4):558. Available at: http://doi.org/10.3390/ijms17040558
24. Wang GY, Zhang L, Geng YD, et al. β-Elemene induces apoptosis and autophagy in colorectal cancer cells through regulating the ROS/AMPK/mTOR pathway. *Chin J Nat Med* 2022;20(1):9–21. Available at: http://doi.org/10.1016/S1875-5364(21)60118-8
25. Zhang D, Zhou Q, Huang D, et al. ROS/JNK/c-Jun axis is involved in oridonin-induced caspase-dependent apoptosis in human colorectal cancer cells. *Biochem Biophys Res Commun* 2019;513(3):594–601. Available at: http://doi.org/10.1016/j.bbrc.2019.04.011
26. Sheikh BY, Sarker MdMR, Kamarudin MNA, Mohan G. Antiproliferative and apoptosis inducing effects of citral via p53 and ROS-induced mitochondrial-mediated apoptosis in human colorectal HCT116 and HT29 cell lines. *Biomed Pharmacother* 2017;96:834–846. Available at: http://doi.org/10.1016/j.biopha.2017.10.038
27. Wang J, Li H, Wang X, Shen T, Wang S, Ren D. Alisol B-23-acetate, a tetracyclic triterpenoid isolated from Alisma orientale, induces apoptosis in human lung cancer cells via the mitochondrial pathway. *Biochem Biophys Res Commun* 2018;505(4):1015–1021. Available at: http://doi.org/10.1016/j.bbrc.2018.10.022
28. Yuan R, Zhao W, Wang QQ, et al. Cucurbitacin B inhibits non-small cell lung cancer in vivo and in vitro by triggering TLR4/NLRP3/GSDMD-dependent pyroptosis. *Pharmacol Res* 2021;170:105748. Available at: http://doi.org/10.1016/j.phrs.2021.105748
29. Sun X, Wang W, Chen J, et al. The Natural Diterpenoid Isoforretin A Inhibits Thioredoxin-1 and Triggers Potent ROS-Mediated Antitumor Effects. *Cancer Res* 2017;77(4):926–936. Available at: http://doi.org/10.1158/0008-5472.CAN-16-0987
30. Geng Y, Zhang C, Lei J, et al. Walsuronoid B induces mitochondrial and lysosomal dysfunction leading to apoptotic rather than autophagic cell death via ROS/p53 signaling pathways in liver cancer. *Biochem Pharmacol* 2017;142:71–86. Available at: http://doi.org/10.1016/j.bcp.2017.06.134
31. Zhang J, Xu Q, Yang HY, Yang M, Fang J, Gao K. Inhibition of Thioredoxin Reductase by Santamarine Conferring Anticancer Effect in HeLa Cells. *Front Mol Biosci* 2021;8:710676. Available at: http://doi.org/10.3389/fmolb.2021.710676
32. Gong G, Shen YL, Lan HY, et al. The Cyr61 Is a Potential Target for Rotundifuran, a Natural Labdane-Type Diterpene from Vitex trifolia L., to Trigger Apoptosis of Cervical Cancer Cells. *Oxid Med Cell Longev* 2021;2021:1–15. Available at: http://doi.org/10.1155/2021/6677687
33. Wang WL, Zhu DR, Chen C, et al. Taicrypnacids A and B, a Pair of C_{37} Heterodimeric Diterpenoid Stereoisomers from Taiwania cryptomerioides. *J Nat Prod* 2019;82(8):2087–2093. Available at: http://doi.org/10.1021/acs.jnatprod.8b00815
34. Liu M, Xiao C, Sun M, Tan M, Hu L, Yu Q. Parthenolide Inhibits STAT3 Signaling by Covalently Targeting Janus Kinases. *Molecules* 2018;23(6):1478. Available at: http://doi.org/10.3390/molecules23061478
35. Zou J, Zhang Y, Sun J, et al. Deoxyelephantopin Induces Reactive Oxygen Species-Mediated Apoptosis and Autophagy in Human Osteosarcoma Cells. *Cell Physiol Biochem* 2017;42(5):1812–1821. Available at: http://doi.org/10.1159/000479537
36. Du J, Wang T, Li Y, et al. DHA inhibits proliferation and induces ferroptosis of leukemia cells through autophagy dependent degradation of ferritin. *Free Radical Biol Med* 2019;131:356–369. Available at: http://doi.org/10.1016/j.freeradbiomed.2018.12.011
37. Cho YS. Genipin, an Inhibitor of UCP2 as a Promising New Anticancer Agent: A Review of the Literature. *Int J Mol Sci* 2022;23(10):5637. Available at: http://doi.org/10.3390/ijms23105637
38. Cai J, Yi M, Tan Y, et al. Natural product triptolide induces GSDME-mediated pyroptosis in head and neck cancer through suppressing mitochondrial hexokinase-II. *J Exp Clin Cancer Res* 2021;40(1):190. Available at: http://doi.org/10.1186/s13046-021-01995-7
39. Park SH, Sung JH, Kim EJ, Chung N. Berberine induces apoptosis via ROS generation in PANC-1 and MIA-PaCa2 pancreatic cell lines. *Braz J Med Biol Res* 2015;48(2):111–119. Available at: http://doi.org/10.1590/1414-431x20144293
40. Zhang B, Wang X, Deng J, et al. p53-dependent upregulation of miR-16-2 by sanguinarine induces cell cycle arrest and apoptosis in hepatocellular carcinoma. *Cancer Lett* 2019;459:50–58. Available at: http://doi.org/10.1016/j.canlet.2019.05.042
41. An K, Zhang Y, Liu Y, et al. Neferine induces apoptosis by modulating the ROS-mediated JNK pathway in esophageal squamous cell carcinoma. *Oncol Rep* 2020;44(3):1116–1126. Available at: http://doi.org/10.3892/or.2020.7675
42. Kung FP, Lim YP, Chao WY, et al. Piperlongumine, a Potent Anticancer Phytotherapeutic, Induces Cell Cycle Arrest and Apoptosis In Vitro and In Vivo through the ROS/Akt Pathway in Human Thyroid Cancer Cells. *Cancers* (*Basel*) 2021;13(17):4266. Available at: http://doi.org/10.3390/cancers13174266
43. Jiang J, Hu C. Evodiamine: A Novel Anti-Cancer Alkaloid from Evodia rutaecarpa. *Molecules* 2009;14(5):1852–1859. Available at: http://doi.org/10.3390/molecules14051852
44. Liu AJ, Wang SH, Chen KC, et al. Evodiamine, a plant alkaloid, induces calcium/JNK-mediated autophagy and calcium/mitochondria-mediated apoptosis in human glioblastoma cells. *Chem Biol Interact* 2013;205(1):20–28. Available at: http://doi.org/10.1016/j.cbi.2013.06.004
45. Lee YJ, Park KS, Nam HS, Cho MK, Lee SH. Apigenin causes necroptosis by inducing ROS accumulation, mitochondrial dysfunction, and ATP depletion in malignant mesothelioma cells. *Korean J Physiol Pharmacol* 2020;24(6):493–502. Available at: http://doi.org/10.4196/kjpp.2020.24.6.493
46. Wang CM, Chen J, Zhao J, et al. Xanthohumol Induces ROS through NADPH Oxidase, Causes Cell Cycle Arrest and Apoptosis. *Oxid Med Cell Longev* 2021;2021:1–12. Available at: http://doi.org/10.1155/2021/9877170
47. Wu J, Wang D, Zhou J, et al. Gambogenic acid induces

apoptosis and autophagy through ROS-mediated endoplasmic reticulum stress via JNK pathway in prostate cancer cells. *Phytother Res* 2022;37(1):310–328. Available at: http://doi.org/10.1002/ptr.7614
48. Raza W, Meena A, Luqman S. 3,5,7-trihydroxyflavone restricts proliferation of androgen-independent human prostate adenocarcinoma cells by inducing ROS-mediated apoptosis and reduces tumour growth. *J Biochem Mol Toxicol* 2023;37(11):e23474. Available at: http://doi.org/10.1002/jbt.23474
49. Wang Z, Ma J, Li X, et al. Quercetin induces p53-independent cancer cell death through lysosome activation by the transcription factor EB and Reactive Oxygen Species-dependent ferroptosis. *Br J Pharmacol* 2021;178(5):1133–1148. Available at: http://doi.org/10.1111/bph.15350
50. Xiao, S, Chen F, Gao C. Anti-tumor activity of 4-O-Methylhonokiol in human oral cancer cells is mediated via ROS generation, disruption of mitochondrial potential, cell cycle arrest and modulation of Bcl-2/Bax proteins. *J BUON* 2017;22(6):1577–1581.
51. Lin CL, Yu CI, Lee TH, et al. Plumbagin induces the apoptosis of drug-resistant oral cancer in vitro and in vivo through ROS-mediated endoplasmic reticulum stress and mitochondrial dysfunction. *Phytomedicine* 2023;111:154655. Available at: http://doi.org/10.1016/j.phymed.2023.154655
52. Dando I, Donadelli M, Costanzo C, et al. Cannabinoids inhibit energetic metabolism and induce AMPK-dependent autophagy in pancreatic cancer cells. *Cell Death Dis* 2013;4(6):e664. Available at: http://doi.org/10.1038/cddis.2013.151
53. Miao Q, Deng W, Lyu W, et al. Erianin inhibits the growth and metastasis through autophagy-dependent ferroptosis in KRASG13D colorectal cancer. *Free Radical Biol Med* 2023;204:301–312. Available at: http://doi.org/10.1016/j.freeradbiomed.2023.05.008
54. Wang H, Zhang T, Sun W, et al. Erianin induces G2/M-phase arrest, apoptosis, and autophagy via the ROS/JNK signaling pathway in human osteosarcoma cells in vitro and in vivo. *Cell Death Dis* 2016;7(6):e2247. Available at: http://doi.org/10.1038/cddis.2016.138
55. Alsamri H, Al Dhaheri Y, Iratni R. Targeting Triple-Negative Breast Cancer by the Phytopolyphenol Carnosol: ROS-Dependent Mechanisms. *Antioxidants* (*Basel*) 2023;12(7):1349. Available at: http://doi.org/10.3390/antiox12071349
56. Chen C, Zhu T, Liu X, et al. Identification of a novel PHGDH covalent inhibitor by chemical proteomics and phenotypic profiling. *Acta Pharm Sin B* 2022;12(1):246–261. Available at: http://doi.org/10.1016/j.apsb.2021.06.008
57. Ahmad G, Mir SA, Anand LK, et al. Myricanol-9-acetate, a Novel Naturally Occurring Derivative of Myricanol, Induces ROS-dependent Mitochondrial-mediated Apoptosis in MCF-7 Cancer Cells. *Curr Top Med Chem* 2021;21(15):1418–1427. Available at: http://doi.org/10.2174/1568026621666210615151358
58. Yang Y, Zhang Y, Wang L, Lee S. Levistolide A Induces Apoptosis via ROS-Mediated ER Stress Pathway in Colon Cancer Cells. *Cell Physiol Biochem* 2017;42(3):929–938. Available at: http://doi.org/10.1159/000478647
59. Geng Y, Liu P, Xie Y, et al. Xanthatin suppresses pancreatic cancer cell growth via the ROS/RBL1 signaling pathway: In vitro and in vivo insights. *Phytomedicine* 2023;119:155004. Available at: http://doi.org/10.1016/j.phymed.2023.155004
60. Szczepańska P, Rychlicka M, Groborz S, et al. Studies on the Anticancer and Antioxidant Activities of Resveratrol and Long-Chain Fatty Acid Esters. *Int J Mol Sci* 2023;24(8):7167. Available at: http://doi.org/10.3390/ijms24087167
61. Liang Q, Wang X, Yang S, et al. Characterization of the antioxidative polysaccharides from Ziziphus jujube cv. Goutouzao and its tumor-inhibitory effects on human colorectal carcinoma LoVo cells via immunocyte activation. *J Food Biochem* 2020;44(11):e13462. Available at: http://doi.org/10.1111/jfbc.13462
62. Li M, Du X, Yuan Z, Cheng M, Dong P, Bai Y. Lentinan triggers oxidative stress-mediated anti-inflammatory responses in lung cancer cells. *Mol Cell Biochem* 2021;477(2):469–477. Available at: http://doi.org/10.1007/s11010-021-04293-0
63. Gersey ZC, Rodriguez GA, Barbarite E, et al. Curcumin decreases malignant characteristics of glioblastoma stem cells via induction of reactive oxygen species. *BMC Cancer* 2017;17(1):99. Available at: http://doi.org/10.1186/s12885-017-3058-2
64. Kundu J, Chae IG, Chun KS. Fraxetin Induces Heme Oxygenase-1 Expression by Activation of Akt/Nrf2 or AMP-activated Protein Kinase α/Nrf2 Pathway in HaCaT Cells. *J Cancer Prev* 2016;21(3):135–143. Available at: http://doi.org/10.15430/JCP.2016.21.3.135
65. Afshari, AR, Jalili-Nik M, Soukhtanloo M, et al. Auraptene-induced cytotoxicity mechanisms in human malignant glioblastoma (U87) cells: role of reactive oxygen species (ROS). *EXCLI J* 2019;18:576–590. Available at: http://doi.org/10.17179/excli2019-1136.
66. Hussain AR, Uddin S, Ahmed M, Al-Dayel F, Bavi PP, Al-Kuraya KS. Phosphorylated I κ Bα Predicts Poor Prognosis in Activated B-Cell Lymphoma and Its Inhibition with Thymoquinone Induces Apoptosis via ROS Release. *PLoS One* 2013;8(3):e60540. Available at: http://doi.org/10.1371/journal.pone.0060540
67. Han X, Han Y, Zheng Y, et al. Chaetocin induces apoptosis in human melanoma cells through the generation of reactive oxygen species and the intrinsic mitochondrial pathway, and exerts its anti-tumor activity in vivo. *PLoS One* 2017;12(4):e0175950. Available at: http://doi.org/10.1371/journal.pone.0175950
68. Perillo B, Di Donato M, Pezone A, et al. ROS in cancer therapy: the bright side of the moon. *Exp Mol Med* 2020;52(2):192–203. Available at: http://doi.org/10.1038/s12276-020-0384-2
69. NavaneethaKrishnan S, Rosales JL, Lee KY. ROS-Mediated Cancer Cell Killing through Dietary Phytochemicals. *Oxid Med Cell Longev* 2019;2019:9051542. Available at: http://doi.org/10.1155/2019/9051542
70. Stieg DC, Wang Y, Liu LZ, Jiang BH. ROS and miRNA Dysregulation in Ovarian Cancer Development, Angiogenesis and Therapeutic Resistance. *Int J Mol Sci* 2022;23(12):6702. Available at: http://doi.org/10.3390/ijms23126702
71. Huang G, Pan ST. ROS-Mediated Therapeutic Strategy in Chemo-/Radiotherapy of Head and Neck Cancer. *Oxid Med Cell Longev* 2020;2020:5047987. Available at: http://doi.org/10.1155/2020/5047987
72. Miller RP, Tadagavadi RK, Ramesh G, Reeves WB. Mechanisms of Cisplatin nephrotoxicity. *Toxins* (*Basel*) 2010;2(11):2490–2518. Available at: http://doi.org/10.3390/toxins2112490
73. Li F, Yao Y, Huang H, Hao H, Ying M. Xanthohumol attenuates cisplatin-induced nephrotoxicity through inhibiting NF- κ B and activating Nrf2 signaling pathways. *Int Immunopharmacol* 2018;61:277–282. Available at: http://doi.org/10.1016/j.intimp.2018.05.017
74. Gan D, He W, Yin H, Gou X. β-elemene enhances cisplatin-induced apoptosis in bladder cancer cells through the ROS-AMPK signaling pathway. *Oncol Lett* 2020;19(1):291–300. Available at:

http://doi.org/10.3892/ol.2019.11103
75. Moussavi M, Haddad F, Rassouli FB, Iranshahi M, Soleymanifard S. Synergy between Auraptene, Ionizing Radiation, and Anticancer Drugs in Colon Adenocarcinoma Cells. *Phytother Res* 2017;31(9):1369–1375. Available at: http://doi.org/10.1002/ptr.5863
76. El-Senduny FF, Badria FA, EL-Waseef AM, Chauhan SC, Halaweish F. Approach for chemosensitization of cisplatin-resistant ovarian cancer by cucurbitacin B. *Tumour Biol* 2016;37(1):685–698. Available at: http://doi.org/10.1007/s13277-015-3773-8
77. Du J, Wang X, Li Y, et al. DHA exhibits synergistic therapeutic efficacy with cisplatin to induce ferroptosis in pancreatic ductal adenocarcinoma via modulation of iron metabolism. *Cell Death Dis* 2021;12(7):705. Available at: http://doi.org/10.1038/s41419-021-03996-y
78. Cao P, Xia Y, He W, et al. Enhancement of oxaliplatin-induced colon cancer cell apoptosis by alantolactone, a natural product inducer of ROS. *Int J Biol Sci* 2019;15(8):1676–1684. Available at: http://doi.org/10.7150/ijbs.35265
79. Kim BR, Jeong YA, Jo MJ, et al. Genipin Enhances the Therapeutic Effects of Oxaliplatin by Upregulating BIM in Colorectal Cancer. *Mol Cancer Ther* 2019;18(4):751–761. Available at: http://doi.org/10.1158/1535-7163.MCT-18-0196
80. Xiang Y, Chen X, Wang W, et al. Natural Product Erianin Inhibits Bladder Cancer Cell Growth by Inducing Ferroptosis via NRF2 Inactivation. *Front Pharmacol* 2021;12:775506. Available at: http://doi.org/10.3389/fphar.2021.775506
81. Su C, Liu S, Ma X, et al. The effect and mechanism of erianin on the reversal of oxaliplatin resistance in human colon cancer cells. *Cell Biol Int* 2021;45(12):2420–2428. Available at: http://doi.org/10.1002/cbin.11684
82. Chen W, Lian W, Yuan Y, Li M. The synergistic effects of oxaliplatin and piperlongumine on colorectal cancer are mediated by oxidative stress. *Cell Death Dis* 2019;10(8):600. Available at: http://doi.org/10.1038/s41419-019-1824-6
83. Ji D, Zhong X, Huang P, et al. Deoxyelephantopin induces apoptosis via oxidative stress and enhances gemcitabine sensitivity in vitro and in vivo through targeting the NF-κB signaling pathway in pancreatic cancer. *Aging* (*Milano*) 2020;12(11):11116–11138. Available at: http://doi.org/10.18632/aging.103327
84. Yang Y, Zhang LJ, Bai XG, Xu HJ, Jin ZL, Ding M. Synergistic antitumour effects of triptolide plus gemcitabine in bladder cancer. *Biomed Pharmacother* 2018;106:1307–1316. Available at: http://doi.org/10.1016/j.biopha.2018.07.083
85. Ye W, Huang Q, Tang T, Qin G. Synergistic effects of piperlongumine and gemcitabine against KRAS mutant lung cancer. *Tumori* 2020;107(2):119–124. Available at: http://doi.org/10.1177/0300891620930789
86. Li G, Fang S, Shao X, et al. Curcumin Reverses NNMT-Induced 5-Fluorouracil Resistance via Increasing ROS and Cell Cycle Arrest in Colorectal Cancer Cells. *Biomolecules* 2021;11(9):1295. Available at: http://doi.org/10.3390/biom11091295
87. Sirangelo I, Liccardo M, Iannuzzi C. Hydroxytyrosol Prevents Doxorubicin-Induced Oxidative Stress and Apoptosis in Cardiomyocytes. *Antioxidants* (*Basel*) 2022;11(6):1087. Available at: http://doi.org/10.3390/antiox11061087
88. Mailloux RJ, Adjeitey CNK, Harper ME. Genipin-Induced Inhibition of Uncoupling Protein-2 Sensitizes Drug-Resistant Cancer Cells to Cytotoxic Agents. *PLoS One* 2010;5(10):e13289. Available at: http://doi.org/10.1371/journal.pone.0013289
89. Kazantseva L, Becerra J, Santos-Ruiz L. Oridonin enhances antitumor effects of doxorubicin in human osteosarcoma cells. *Pharmacol Rep* 2021;74(1):248–256. Available at: http://doi.org/10.1007/s43440-021-00324-1
90. Chae IG, Song NY, Kim DH, Lee MY, Park JM, Chun KS. Thymoquinone induces apoptosis of human renal carcinoma Caki-1 cells by inhibiting JAK2/STAT3 through pro-oxidant effect. *Food Chem Toxicol* 2020;139:111253. Available at: http://doi.org/10.1016/j.fct.2020.111253
91. Fatfat M, Fakhoury I, Habli Z, Mismar R, Gali-Muhtasib H. Thymoquinone enhances the anticancer activity of doxorubicin against adult T-cell leukemia in vitro and in vivo through ROS-dependent mechanisms. *Life Sci* 2019;232:116628. Available at: http://doi.org/10.1016/j.lfs.2019.116628
92. Awasthee N, Shekher A, Rai V, et al. Piperlongumine, a piper alkaloid, enhances the efficacy of doxorubicin in breast cancer: involvement of glucose import, ROS, NF-κB and lncRNAs. *Apoptosis* 2022;27(3–4):261–282. Available at: http://doi.org/10.1007/s10495-022-01711-6
93. Xu Y, Xin Y, Diao Y, et al. Synergistic effects of apigenin and paclitaxel on apoptosis of cancer cells. *PLoS One* 2011;6(12):e29169. Available at: http://doi.org/10.1371/journal.pone.0029169
94. Liu W, Gu J, Qi J, et al. Lentinan exerts synergistic apoptotic effects with paclitaxel in A549 cells via activating ROS-TXNIP-NLRP3 inflammasome. *J Cell Mol Med* 2015;19(8):1949–1955. Available at: http://doi.org/10.1111/jcmm.12570
95. Qu Y, Cong P, Lin C, Deng Y, Li-Ling J, Zhang M. Inhibition of paclitaxel resistance and apoptosis induction by cucurbitacin B in ovarian carcinoma cells. *Oncol Lett* 2017;14(1):145–152. Available at: http://doi.org/10.3892/ol.2017.6148
96. Zhang X, Huang J, Yu C, et al. Quercetin Enhanced Paclitaxel Therapeutic Effects Towards PC-3 Prostate Cancer Through ER Stress Induction and ROS Production. *Onco Targets Ther* 2020;13:513–523. Available at: http://doi.org/10.2147/OTT.S228453
97. Rawat L, Hegde H, Hoti SL, Nayak V. Piperlongumine induces ROS mediated cell death and synergizes paclitaxel in human intestinal cancer cells. *Biomed Pharmacother* 2020;128:110243. Available at: http://doi.org/10.1016/j.biopha.2020.110243
98. Lei CS, Hou YC, Pai MH, Lin MT, Yeh SL. Effects of quercetin combined with anticancer drugs on metastasis-associated factors of gastric cancer cells: in vitro and in vivo studies. *J Nutr Biochem* 2018;51:105–113. Available at: http://doi.org/10.1016/j.jnutbio.2017.09.011
99. Tan BL, Norhaizan ME. Curcumin Combination Chemotherapy: The Implication and Efficacy in Cancer. *Molecules* 2019;24(14):2527. Available at: http://doi.org/10.3390/molecules24142527
100. Chen P, Li X, Zhang R, et al. Combinative treatment of β-elemene and cetuximab is sensitive to KRAS mutant colorectal cancer cells by inducing ferroptosis and inhibiting epithelial-mesenchymal transformation. *Theranostics* 2020;10(11):5107–5119. Available at: http://doi.org/10.7150/thno.44705
101. Kang N, Cao S, Jiang B, et al. Cetuximab enhances oridonin-induced apoptosis through mitochondrial pathway and endoplasmic reticulum stress in laryngeal squamous cell carcinoma cells. *Toxicol In Vitro* 2020;67:104885. Available at: http://doi.org/10.1016/j.tiv.2020.104885
102. Liu C, Sun S, Feng Q, et al. Arsenene Nanodots with Selective Killing Effects and their Low-Dose Combination with ß-Elemene for Cancer Therapy. *Adv Mater* 2021;33(37):e2102054. Available at:

http://doi.org/10.1002/adma.202102054
103. Cai X, Miao J, Sun R, et al. Dihydroartemisinin overcomes the resistance to osimertinib in EGFR-mutant non-small-cell lung cancer. *Pharmacol Res* 2021;170:105701. Available at: http://doi.org/10.1016/j.phrs.2021.105701
104. Kim SH, Kang JG, Kim CS, Ihm SH, Choi MG, Lee SJ. Evodiamine in combination with histone deacetylase inhibitors has synergistic cytotoxicity in thyroid carcinoma cells. *Endocrine* 2019;65(1):110–120. Available at: http://doi.org/10.1007/s12020-019-01885-1
105. Liang Y, Liu ZY, Wang PY, Li YJ, Wang RR, Xie SY. Nanoplatform-based natural products co-delivery system to surmount cancer multidrug-resistant. *J Controlled Release* 2021;336:396–409. Available at: http://doi.org/10.1016/j.jconrel.2021.06.034
106. Liu Y, Shi C, He Z, et al. Inhibition of PI3K/AKT signaling via ROS regulation is involved in Rhein-induced apoptosis and enhancement of oxaliplatin sensitivity in pancreatic cancer cells. *Int J Biol Sci* 2021;17(2):589–602. Available at: http://doi.org/10.7150/ijbs.49514
107. Cen K, Chen M, He M, et al. Sporoderm-Broken Spores of Ganoderma lucidum Sensitizes Ovarian Cancer to Cisplatin by ROS/ERK Signaling and Attenuates Chemotherapy-Related Toxicity. *Front Pharmacol* 2022;13:826716. Available at: http://doi.org/10.3389/fphar.2022.826716
108. Zhang W, Li S, Li C, Li T, Huang Y. Remodeling tumor microenvironment with natural products to overcome drug resistance. *Front Immunol* 2022;13:1051998. Available at: http://doi.org/10.3389/fimmu.2022.1051998
109. Budi HS, Farhood B. Tumor microenvironment remodeling in oral cancer: Application of plant derived-natural products and nanomaterials. *Environ Res* 2023;233:116432. Available at: http://doi.org/10.1016/j.envres.2023.116432
110. Su LJ, Zhang JH, Gomez H, et al. Reactive Oxygen Species-Induced Lipid Peroxidation in Apoptosis, Autophagy, and Ferroptosis. *Oxid Med Cell Longev* 2019;2019:5080843. Available at: http://doi.org/10.1155/2019/5080843
111. Ying JF, Lu ZB, Fu LQ, et al. The role of iron homeostasis and iron-mediated ROS in cancer. *Am J Cancer Res* 2021;11(5):1895–1912.
112. Pang L, Zhang L, Zhou H, Cao L, Shao Y, Li T. Reactive Oxygen Species-Responsive Nanococktail With Self-Amplificated Drug Release for Efficient Co-Delivery of Paclitaxel/Cucurbitacin B and Synergistic Treatment of Gastric Cancer. *Front Chem* 2022;10:844426. Available at: http://doi.org/10.3389/fchem.2022.844426