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

Shu-Fan Wang¹, Shi-Qi Dong¹, Quan Dong³, Wen-Xin Lin¹, Mei Dong⁴, Duo Liu¹*⁵

¹Department 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.

Acknowledgments
This study was supported by National Natural Science Foundation of China (No. 82003775), Talent Project established by Chinese Pharmaceutical Association Hospital Pharmacy department. (No. CPA-205-ZC-2023-003), Outstanding Young Scholars Foundation of Harbin Medical University Cancer Hospital (No. JQ2021-04), Heilongjiang Province postdoctoral research fund (No. LBH-Q20050), and Special fund for clinical and basic research of medical research development fund (No. YXXY-W50135).

Peer review information
Traditional Medicine Research thanks all anonymous reviewers for their contribution to the peer review of this paper.

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

Citation

Received: 30 June 2023; Accepted: 27 November 2023;
Available online: 28 November 2023
© 2024 By Author(s). Published by TMR Publishing Group Limited. This is an open access article under the CC-BY license. (https://creativecommons.org/licenses/by/4.0/)

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

Submit a manuscript: https://www.tmrjournals.com/tmr
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 tumorogenesis [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$_2^-$), hydroxyl radicals (OH) and hydrogen peroxide (H$_2$O$_2$) [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-Isneid selected sesquiterpenes 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.
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 phosphatidyserine, 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]. Walsuwaroin B enhances the production of hydrogen peroxide, nitric oxide, and superoxide anion radicals, resulting in elevated ROS levels. In addition, Walsuwaroin B induced ROS to upregulate p53 levels, and ROS and sanguinarine 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. Taecrypyrones induce a significant and dose-dependent increase in intracellular Ca²⁺ concentration and ROS levels, with vacuole-like morphological changes in the endoplasmic reticulum, which serves as a Ca²⁺ 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.** Decoyxelthalopin (DET), the active ingredient in Elephantops 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 aspartate activation [35]. Dihydrorhizemisin (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 leukemia 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 antitumor 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]. Tripolide, 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.** Evidiolamine is a major alkaloid isolated from Evidia rutharcarpa Bentham, with a variety of pharmacological activities. Liu found that evidiolamine 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 fruits and vegetables. This 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 gabemogenic acid significantly promoted ROS production and endoplasmic reticulum stress. Gambogic 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]. ErIan 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 Xanthin on pancreatic cancer and its molecular mechanisms. Xanthin prevented the proliferation and metastasis of pancreatic cancer cells and triggered phosphatidylinerine 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 Goutouza's study, Liang showed that it enhanced the viability of mouse mononuclear macrophages, activated the immune response, and increased intracellular ROS to induce apoptosis in colorectal cancer cells [61]. Lentimin is a potent active ingredient extracted from high-quality shiitake mushroom seeds. In the study of Li, the mechanism of anti-inflammatory function of Lentimin in lung cancer cells was investigated. Lentimin 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 CMH2DCFDA 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>
<thead>
<tr>
<th>Category</th>
<th>Nature product</th>
<th>Source species</th>
<th>Cancer type</th>
<th>Target cell lines</th>
<th>Pathway</th>
<th>Time/dose dependence</th>
<th>Cell cycle block</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terpenoids</td>
<td>alantolactone (ATL)</td>
<td>Inula helemium</td>
<td>Colon cancer</td>
<td>SW480 &amp; SW1116 Colorectal cancer cells</td>
<td>/</td>
<td>/</td>
<td>G1</td>
<td>[23]</td>
</tr>
<tr>
<td></td>
<td>β-elemene</td>
<td>turmeric</td>
<td>Colon cancer</td>
<td>MDA-MB-231 cells</td>
<td>ROS/AMPK/mTOR pathway</td>
<td>/</td>
<td>G2/M</td>
<td>[24]</td>
</tr>
<tr>
<td></td>
<td>oridonin</td>
<td>Rubusosia rubescens</td>
<td>/</td>
<td>CRC cells</td>
<td>ROS/JNK/c-Jun pathway</td>
<td>/</td>
<td>/</td>
<td>[25]</td>
</tr>
<tr>
<td></td>
<td>citral</td>
<td>Plants with lemon scent</td>
<td>/</td>
<td>HCT116 &amp; HT29 cells</td>
<td>p53/ROS pathway</td>
<td>/</td>
<td>/</td>
<td>[26]</td>
</tr>
<tr>
<td></td>
<td>Alisol B-23-acetate</td>
<td>Alistia orientale</td>
<td>Lung cancer</td>
<td>A549 &amp; NCI-H292 cells</td>
<td>Mitochondrial pathway</td>
<td></td>
<td>Dose-depend</td>
<td>[27]</td>
</tr>
<tr>
<td></td>
<td>Cucurbitacin B (CBB)</td>
<td>muskmelon pedicel</td>
<td>Lung cancer</td>
<td>NSCLC cells</td>
<td>TLR4/NLRP3/GSD MD</td>
<td></td>
<td>/</td>
<td>[28]</td>
</tr>
<tr>
<td></td>
<td>Isoforretin A</td>
<td>Isodon forrestii</td>
<td>Liver cancer</td>
<td>HepG2 cells</td>
<td>Inhibit Trx1</td>
<td>/</td>
<td>/</td>
<td>[29]</td>
</tr>
<tr>
<td></td>
<td>Santamarine</td>
<td>Ambrosia confertiflora</td>
<td>Cervical cancer</td>
<td>HeLa cells</td>
<td>Target TrxR</td>
<td>/</td>
<td>/</td>
<td>[31]</td>
</tr>
<tr>
<td></td>
<td>Rotundifuran</td>
<td>Vitex trifolia</td>
<td>Cervical cancer</td>
<td>HeLa &amp; SiHa cells</td>
<td>MAPK &amp; PI3K/Akt pathway</td>
<td>/</td>
<td>/</td>
<td>[32]</td>
</tr>
<tr>
<td></td>
<td>Taiicryptacids</td>
<td>Taiwania cryptomeriodes</td>
<td>/</td>
<td>MCF-7 &amp; HCT-116 cells</td>
<td>Ca2+/ROS pathway</td>
<td></td>
<td>Dose-depend</td>
<td>[33]</td>
</tr>
<tr>
<td></td>
<td>Parthenolide</td>
<td>Feverfew</td>
<td>/</td>
<td>HEK293 cells</td>
<td>Inhibit JAK/STAT3 signal transduction</td>
<td>/</td>
<td>/</td>
<td>[34]</td>
</tr>
<tr>
<td></td>
<td>Densylephantopin</td>
<td>Eupiphantus scaber</td>
<td>Osteosarcoma</td>
<td>Osteosarcoma cells</td>
<td>Inhibit NF-κ B activation</td>
<td></td>
<td>Dose-depend</td>
<td>[35]</td>
</tr>
<tr>
<td></td>
<td>Dihydroartemisinin</td>
<td>Artemisia annua</td>
<td>Leukemia</td>
<td>AML cells</td>
<td>AMPK/mTOR/p70 S6k pathway</td>
<td>/</td>
<td>G0/G1</td>
<td>[36]</td>
</tr>
<tr>
<td></td>
<td>Genipin</td>
<td>Gardenia jasminoides</td>
<td>/</td>
<td>/</td>
<td>ROS/JNK/c-Jun pathway</td>
<td></td>
<td>/</td>
<td>[37]</td>
</tr>
<tr>
<td></td>
<td>Triptolide</td>
<td>Tripterygium wilfordii Hook f</td>
<td>Head &amp; neck cancer</td>
<td>Head and neck cancer cells</td>
<td>Inhibit NRF2 / SLC7A11 pathway</td>
<td>/</td>
<td>/</td>
<td>[38]</td>
</tr>
<tr>
<td>Alkaloids</td>
<td>Berberine</td>
<td>berberis</td>
<td>Pancreatic cancer</td>
<td>PANC-1 &amp; MIA-PaCa2 cells</td>
<td>/</td>
<td></td>
<td>Dose-depend</td>
<td>G1</td>
</tr>
<tr>
<td></td>
<td>Sanguinarine</td>
<td>Sanguinaria canadensis</td>
<td>Liver cancer</td>
<td>HCC cells</td>
<td>p53/ROS pathway</td>
<td>/</td>
<td>/</td>
<td>[40]</td>
</tr>
<tr>
<td></td>
<td>Neferine</td>
<td>Nelumbo nucifera</td>
<td>Esophageal Cancer</td>
<td>ESCC cells</td>
<td>ROS/JNK/c-Jun pathway</td>
<td>/</td>
<td>G2/M</td>
<td>[41]</td>
</tr>
<tr>
<td></td>
<td>Piperlongumine</td>
<td>long pepper</td>
<td>Thyroid cancer</td>
<td>TC cell lines</td>
<td>Inhibit Akt/mTOR pathway</td>
<td></td>
<td>Time &amp; dose-depend</td>
<td>[42]</td>
</tr>
<tr>
<td></td>
<td>Evodiamine</td>
<td>Evodia ratatacarpa Bentham</td>
<td>Glioblastoma</td>
<td>Glioblastoma cells</td>
<td>Ca2+/JNK pathway</td>
<td>/</td>
<td>G2/M</td>
<td>[41, 42]</td>
</tr>
<tr>
<td></td>
<td>Apigenin</td>
<td>Celery</td>
<td>Malignant mesothelioma</td>
<td>MSTD-211H &amp; H2452 cells</td>
<td>/</td>
<td></td>
<td>/</td>
<td>G2/M</td>
</tr>
<tr>
<td></td>
<td>Xanthohumol</td>
<td>Humulus lupulus</td>
<td>Acute myeloid leukemia</td>
<td>HL-60 cells</td>
<td>/</td>
<td></td>
<td>G1 phase</td>
<td>[46]</td>
</tr>
<tr>
<td></td>
<td>Quercetin</td>
<td>Multiple plants</td>
<td>/</td>
<td>Various cancer cell lines</td>
<td>transcription factor EB-ROS mediates</td>
<td>/</td>
<td>/</td>
<td>[49]</td>
</tr>
<tr>
<td></td>
<td>Gambogenic acid</td>
<td>Gamboge</td>
<td>Prostate cancer</td>
<td>PC3 and DU145 cells</td>
<td>JNK pathway</td>
<td>/</td>
<td>/</td>
<td>[47]</td>
</tr>
<tr>
<td></td>
<td>3,5,7-trihydroxyflavone</td>
<td>/</td>
<td>Prostate cancer</td>
<td>EAC cells</td>
<td>Mitochondria-mediated apoptosis</td>
<td></td>
<td>Time &amp; dose-depend</td>
<td>G2/M</td>
</tr>
<tr>
<td>Phenolic</td>
<td>4-O-Methylhonokiol</td>
<td>Magnolia officinalis</td>
<td>Oral cancer</td>
<td>OSCC PE/CA-PJ41 cells</td>
<td>/</td>
<td></td>
<td>Dose-depend</td>
<td>G2/M</td>
</tr>
</tbody>
</table>
Table 1 Natural compounds with anti-tumor effect by increasing ROS (continued)

<table>
<thead>
<tr>
<th>Category</th>
<th>Nature product</th>
<th>Source species</th>
<th>Cancer type</th>
<th>Target cell lines</th>
<th>Pathway</th>
<th>Time/dose dependence</th>
<th>Cell cycle block</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cannabinoids</td>
<td>Cannabis</td>
<td></td>
<td>Pancreatic cancer</td>
<td>Panc1 cells</td>
<td>Akt/c-Myc pathway</td>
<td>/</td>
<td>/</td>
<td>[52]</td>
</tr>
<tr>
<td>Erianin</td>
<td>Dendrobium</td>
<td></td>
<td>Osteosarcoma cells</td>
<td>Osteosarcoma cells</td>
<td>ROS/JNK pathway</td>
<td>/</td>
<td>G2/M</td>
<td>[54]</td>
</tr>
<tr>
<td>Phytochemicals</td>
<td>Rosemary</td>
<td></td>
<td>Triple-negative breast cancer</td>
<td>MDA-MB-72 cells</td>
<td>MAPK pathway</td>
<td>Dose-dependent</td>
<td>G2</td>
<td>[55]</td>
</tr>
<tr>
<td>Erianin</td>
<td>Honeysuckle</td>
<td></td>
<td>Colorectal cancer</td>
<td>CRC cells</td>
<td>Ras/Raf/ERK pathway</td>
<td>Dose-dependent</td>
<td>/</td>
<td>[53]</td>
</tr>
<tr>
<td>Plumbagin</td>
<td>Plumbago zeylanica L</td>
<td></td>
<td>Oral cancer</td>
<td>CR-SAS cells</td>
<td>ER stress pathway</td>
<td>/</td>
<td>/</td>
<td>[51]</td>
</tr>
<tr>
<td>Esters</td>
<td>withangulatin A</td>
<td>Physalis angulata</td>
<td>/</td>
<td>ZR-75-1, HCT-116 &amp; MCF-7 breast cancer cells</td>
<td>Induces PHGDH inactivation</td>
<td>/</td>
<td>/</td>
<td>[56]</td>
</tr>
<tr>
<td>Myricanol-9-acetate</td>
<td>Myricanol</td>
<td></td>
<td>/</td>
<td>MCF-7 breast cancer cells</td>
<td>/</td>
<td>Dose-dependent</td>
<td>G0/G1</td>
<td>[57]</td>
</tr>
<tr>
<td>Levistolide A</td>
<td>Ligusticum chaixiong Hort</td>
<td></td>
<td>Colon cancer</td>
<td>HCT116 cells</td>
<td>ROS-mediated ER stress pathway</td>
<td>/</td>
<td>/</td>
<td>[58]</td>
</tr>
<tr>
<td>Resveratrol</td>
<td>Resveratrol</td>
<td></td>
<td>Lung cancer</td>
<td>A549 cells and HT29 cells</td>
<td>pro-apoptotic pathways (p21, p53, and Bak)</td>
<td>Dose-dependent</td>
<td>/</td>
<td>[60]</td>
</tr>
<tr>
<td>Xanthatin</td>
<td>Xanthium strumarium L</td>
<td></td>
<td>Pancreatic cancer</td>
<td>BxPC-3 and PANC-1 cells</td>
<td>ROS/RB1 signal pathway</td>
<td>Dose-dependent</td>
<td>/</td>
<td>[59]</td>
</tr>
<tr>
<td>Polysaccharide</td>
<td>Goutouza</td>
<td>Ziziphus jujube</td>
<td>Colorectal cancer</td>
<td>LoVo cells</td>
<td>Activating the immune response</td>
<td>/</td>
<td>G0/G1</td>
<td>[61]</td>
</tr>
<tr>
<td>Polysaccharide</td>
<td>Lentinan</td>
<td>Lentinula edodes</td>
<td>Lung cancer</td>
<td>A549 cells</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>[62]</td>
</tr>
<tr>
<td>Diketones</td>
<td>Curcumin</td>
<td>Turmeric</td>
<td>Glioblastoma</td>
<td>Glioblastoma stem cells</td>
<td>MAPK pathway</td>
<td>Dose-dependent</td>
<td>/</td>
<td>[63]</td>
</tr>
<tr>
<td>Coumarins</td>
<td>Fraxetin</td>
<td>Praxina borneana A.DC.</td>
<td></td>
<td>HaCaT cells</td>
<td>Akt/NFκB2 pathway</td>
<td>Dose-dependent</td>
<td>/</td>
<td>[64]</td>
</tr>
<tr>
<td>Diketopiperazines</td>
<td>chaetocin</td>
<td>fungi</td>
<td>Melanoma</td>
<td>Sk-Mel-28 &amp; A375 cells</td>
<td>Mitochondrial pathway</td>
<td>Time &amp; dose-dependent</td>
<td>/</td>
<td>[65]</td>
</tr>
<tr>
<td>/</td>
<td>Auraptene</td>
<td>Citrus</td>
<td>Malignant glioma</td>
<td>U87 cells</td>
<td>/</td>
<td>Dose-dependent</td>
<td>/</td>
<td>[66]</td>
</tr>
<tr>
<td>Phytochemicals</td>
<td>Thymoquinone</td>
<td>Nigella sativa</td>
<td>Lymphoma</td>
<td>ABC-DLBCL cell lines</td>
<td>Inhibit NFκB activation</td>
<td>/</td>
<td>/</td>
<td>[67]</td>
</tr>
</tbody>
</table>

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 etarin 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 etarin 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 antitumor 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 polymerase and thymidine nucleoside synthesis, 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 LC3-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 nuclear 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. Hydroxyurea is able to counteract adriamycin-induced cytotoxicity in cardiomyocytes by acting on SOD2 levels and oxidative responses and apoptotic mechanisms mediated by Be-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 Lentinian via ROS has been demonstrated, while co-treatment with paclitaxel and Lentinian further triggered ROS production and increased thioedxoin-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, as such 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, phenoxodiol 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 Ganfu tablet. 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-tumor 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>
<thead>
<tr>
<th>Nature product</th>
<th>Chemotherapy drugs</th>
<th>Combination effect</th>
<th>Tumor type</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apigenin</td>
<td>Paclitaxel</td>
<td>Synergistic anti-tumor</td>
<td>Cervical cancer</td>
<td>[93]</td>
</tr>
<tr>
<td>Deoxyelephantopin</td>
<td>Gemcitabine</td>
<td>Synergistic anti-tumor</td>
<td>Pancreatic cancer</td>
<td>[83]</td>
</tr>
<tr>
<td>Alantolactone</td>
<td>Oxaliplatin</td>
<td>Synergistic anti-tumor</td>
<td>Colon cancer</td>
<td>[78]</td>
</tr>
<tr>
<td>Lentinan</td>
<td>Paclitaxel</td>
<td>Synergistic anti-tumor</td>
<td>Lung cancer</td>
<td>[94]</td>
</tr>
<tr>
<td>Xanthohumol</td>
<td>Cisplatin</td>
<td>Reduction of nephrotoxicity</td>
<td></td>
<td>[73]</td>
</tr>
<tr>
<td>β-elemene</td>
<td>Cetuximab</td>
<td>Synergistic anti-tumor</td>
<td>Colorectal cancer</td>
<td>[100]</td>
</tr>
<tr>
<td></td>
<td>Cisplatin</td>
<td>Synergistic anti-tumor</td>
<td>Bladder cancer</td>
<td>[74]</td>
</tr>
<tr>
<td>Arsenic-based drugs</td>
<td>Synergistic anti-tumor</td>
<td>Solid tumor</td>
<td></td>
<td>[102]</td>
</tr>
<tr>
<td>Auraptene</td>
<td>Cisplatin</td>
<td>Synergistic anti-tumor</td>
<td>Colon adenocarcinoma</td>
<td>[75]</td>
</tr>
<tr>
<td>Cucurbetaxin B</td>
<td>Cisplatin</td>
<td>Synergistic anti-tumor</td>
<td>Ovarian cancer</td>
<td>[76]</td>
</tr>
<tr>
<td>Curcumin</td>
<td>Paclitaxel</td>
<td>Reducing drug resistance</td>
<td>Ovarian carcinoma</td>
<td>[95]</td>
</tr>
<tr>
<td></td>
<td>Adriamycin</td>
<td>Synergistic anti-tumor</td>
<td>Colon cancer</td>
<td>[99]</td>
</tr>
<tr>
<td></td>
<td>Gispatin</td>
<td>Synergistic anti-tumor</td>
<td>Liver cancer</td>
<td>[99]</td>
</tr>
<tr>
<td></td>
<td>Docetaxel</td>
<td>Synergistic anti-tumor</td>
<td>Breast cancer</td>
<td>[99]</td>
</tr>
<tr>
<td>Dihydroartemisinin</td>
<td>Cisplatin</td>
<td>Synergistic anti-tumor</td>
<td>Pancreatic cancer</td>
<td>[77]</td>
</tr>
<tr>
<td></td>
<td>Ocetinib</td>
<td>Reducing drug resistance</td>
<td>Lung cancer</td>
<td>[103]</td>
</tr>
<tr>
<td>Hydroxytyrosol</td>
<td>Adriamycin</td>
<td>Reduces cardiotoxicity</td>
<td>Osteosarcoma</td>
<td>[87]</td>
</tr>
<tr>
<td>Genipin</td>
<td>Oxaliplatin</td>
<td>Synergistic anti-tumor</td>
<td>Colorectal cancer</td>
<td>[79]</td>
</tr>
<tr>
<td></td>
<td>Menauquinone</td>
<td>Reducing drug resistance</td>
<td>Leukemia</td>
<td>[88]</td>
</tr>
<tr>
<td></td>
<td>Adriamycin</td>
<td>Reducing drug resistance</td>
<td>Leukemia</td>
<td>[88]</td>
</tr>
<tr>
<td></td>
<td>Epirubicin</td>
<td>Reducing drug resistance</td>
<td>Leukemia</td>
<td>[88]</td>
</tr>
<tr>
<td>Erianin</td>
<td>Oxaliplatin</td>
<td>Reducing drug resistance</td>
<td>Colon cancer</td>
<td>[81]</td>
</tr>
<tr>
<td>Evodiamine</td>
<td>Belinostat</td>
<td>Synergistic anti-tumor</td>
<td>Thyroid carcinoma</td>
<td>[104]</td>
</tr>
<tr>
<td>Triptolide</td>
<td>Gemcitabine</td>
<td>Synergistic anti-tumor</td>
<td>Bladder cancer</td>
<td>[84]</td>
</tr>
<tr>
<td>Oridinon</td>
<td>Cetuximab</td>
<td>Synergistic anti-tumor</td>
<td>Laryngeal cancer</td>
<td>[101]</td>
</tr>
<tr>
<td></td>
<td>Adriamycin</td>
<td>Synergistic anti-tumor</td>
<td>Osteosarcoma</td>
<td>[89]</td>
</tr>
<tr>
<td>Thymoquinone</td>
<td>Adriamycin</td>
<td>Synergistic anti-tumor</td>
<td>Leukemia</td>
<td>[91]</td>
</tr>
<tr>
<td>Quercetin</td>
<td>Irinotecan</td>
<td>Synergistic anti-tumor</td>
<td>Gastric cancer</td>
<td>[98]</td>
</tr>
<tr>
<td></td>
<td>Paclitaxel</td>
<td>Synergistic anti-tumor</td>
<td>Prostate cancer</td>
<td>[96]</td>
</tr>
<tr>
<td>Piperlongumine</td>
<td>Paclitaxel</td>
<td>Synergistic anti-tumor</td>
<td>Intestinal cancer</td>
<td>[97]</td>
</tr>
<tr>
<td></td>
<td>Gemcitabine</td>
<td>Synergistic anti-tumor</td>
<td>Lung cancer</td>
<td>[85]</td>
</tr>
<tr>
<td></td>
<td>Oxaliplatin</td>
<td>Synergistic anti-tumor</td>
<td>Colorectal cancer</td>
<td>[82]</td>
</tr>
<tr>
<td></td>
<td>Adriamycin</td>
<td>Synergistic anti-tumor</td>
<td>Breast cancer</td>
<td>[92]</td>
</tr>
</tbody>
</table>
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 polyethylene glycolated arsenic nanodots that can selectively and effectively treat solid tumors, and polyethylene glycolated 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 pericellular material micelles and once it enters cancer cells, pericellular 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 ananchronic 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
http://doi.org/10.2174/156809616666160216125833
42. Kung FP, Lim YP, Chao WY, et al. Piperlongumine, a Potent Anticancer Phytotherapeutic, Induces Cell Cycle Arrest and Apoptosis In Vivo 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/cancers13172466

Submit a manuscript: https://www.tmrjournals.com/tmr


Submit a manuscript: https://www.tmrjournals.com/tmr
http://doi.org/10.3892/ol.2019.11103


Submit a manuscript: https://www.tmrjournals.com/tmr

13


