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Natural compounds targeting cellular redox homeostasis in malignancies

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ABSTRACT

Malignant tumors are one of the diseases that are most threatening to the health of people and their lives. Moreover, it has already had a great impact on social and financial problems. With the further development of science and technology, the therapeutic approaches to malignant tumors are becoming more and more effective. At present, the common therapies for malignant tumors include surgical resections, radiotherapy, targeted therapy, and immunotherapy, which contribute to effectively suppressing tumor progression. However, these treatments showed severe side effects and complications. Over the last few decades, clinicians and researchers have found that chemical compounds extracted from natural products may be useful for treating cancer. Natural compounds like paclitaxel, doxorubicin, and camptothecin, have been successfully used to treat lung cancer as chemotherapeutic medicine. Numerous new natural compounds have been discovered that can be used to treat malignant tumors. As we know, the reactive oxygen species (ROS) closely connect to the occurrence, development, and apoptosis of tumors. The concentration of ROS in tumor cells plays an important role in the growth and development of tumors. In this review, we present a summary of some natural compounds that modulate redox homeostasis. They are promising candidates for the treatment option for cancer. Moreover, we have also explained the mechanism of the pharmacological reactions of natural compounds affiliated with ROS. It is hoped that new solutions can be provided for drug treatment of tumors.

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Introduction

Malignant tumors are a major health problem worldwide that seriously threatens the health of people. It has already brought many challenges in terms of politics, economy, culture, and society. At the end of 2018, it was estimated that 17 million new cancer cases had been diagnosed and over half of these patients ended up to death. Furthermore, the reports show that the new cases will rise to 27,5 million by 2040 (1). The most common methods for treating malignant tumors are surgery, chemotherapy, radiotherapy, and immunotherapy. These treatments have a positive effect on the killing of tumor cells, but these methods typically have serious toxic side effects and expensive treatment costs. For example, surgery is usually used to treat early-stage cancer patients and is associated with a high risk of cancer recurrence. Radiotherapy may decrease the immune system and cause hypersensitivity, and chemotherapy may kill the normal cells simultaneously. However, severe adverse reactions and drug resistance are still the main obstacles to successful treatment when using these drugs. In recent years, scientists have focused on identifying natural compounds with lower toxicity that can function as reagents to cure human diseases (2-9). Like, bacterial cellulose (BC) was successfully produced by using wasted rotten tomatoes, which effectively inhibited the growth of bacteria, indicating a green and low-cost development of healthcare biomaterials (10). Additionally, in malignant tumors, scientists have also found some natural compounds to treat the cancer and prolong people's survival time. Traditional Chinese medicine (TCM), widely used by patients with cancers in China, can deflect the immune escape of tumors by amending the microenvironment and enhancing the function of the immune system (11, 12). Natural compounds can inhibit tumor growth by promoting apoptosis of tumor cells, with a potential for tumor angiogenesis and reducing tumor cell resistance, extending patient survival, improving clinical symptoms, and raising patients' quality of life. For instance, triterpenoid compounds (TCs) possess good antioxidant and antitumor activities (13). The TCs obtained from Morchella mycelium significantly suppressed the proliferation of PC-3, HT-29, HepG2, HeLa, and HepG2 cell lines (14). Clinical data have shown that the nanoformulation of albumin-PTX (nab-PTX) plus gemcitabine improved the overall survival and response rates compared with gemcitabine alone in pancreatic ductal carcinoma patients (15). A retrospective study of 65 patients showed that nab-PTX combined with a gemcitabine regimen significantly decreased the density of tumor activity (16). Some natural compounds have been found to eliminate tumor cells through autophagy, apoptosis, and a variety of signal pathways, among which reactive oxygen species (ROS) driven oxidative stress is particularly important to destroy tumors. Redox homeostasis is the basis for maintaining the normal metabolism of cells. The ROS level in tumor cells is higher than in normal cells, and tumor cells have some

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characteristic changes to adapt to their high ROS level. It is believed that interference with ROS homeostasis can disrupt the biological metabolism of cancer cells and effectively induce apoptosis of cancer cells. This study summarizes the mechanisms and prospects for the application of natural compounds targeting cellular redox homeostasis in the treatment of malignancies.

Cellular redox homeostasis

ROS production and elimination

ROS refers to certain metabolites in the organism and their derived oxygen-containing substances, including free radical and non-free radical types (17). A radical type of free radical such as superoxide anion ($O_2^{\bullet-}$), high reactive hydroxyl radical ($OH^{\bullet}$), peroxy radical ($ROO^{\bullet}$), as well as mercaptoperoxy radical ($RSOO^{\bullet}$). Non-free radicals include ozone (O_3), hydrogen peroxide (H_2O_2), organic hydroperoxide (ROOH), and singlet oxygen ($^1O_2$) (18). These ROS are oxygen derivatives with a class of strong chemical activity. As shown in Figure 1, mitochondria are the principal site of ROS production and cell metabolism. Complexes I, II, and III of the mitochondrial electron transport chain (ETC) in the mitochondrial inner membrane are major sites of ROS production from mitochondria. ETC could transfer electrons from nicotinamide adenine dinucleotide (NADH) to oxygen molecules (O_2) and the incomplete reduction of oxygen leads to the production of $O_2^{\bullet-}$. Part of $O_2^{\bullet-}$ enter the voltage-dependent anion channels (VDAC) in to cytosol, and $O_2^{\bullet-}$ can also through superoxide dismutase (SOD) into H_2O_2 (19). Myeloperoxidase (MPO) could transform H_2O_2 into hypochlorous acid (HCLO); H_2O_2 is converted to $OH^{\bullet}$ by the Fenton reaction under the action of copper and iron ions. Some enzymes also produce ROS, such as nicotinamide adenine dinucleotide phosphate (NADPH) oxidases (NOXs). NOXs transfer electrons from NADH to O_2 to produce ROS (20). Xanthine oxidase (XO), nitric oxide synthase (NOS) enzymes, lipoxygenases, and cytochrome P450 have also produced ROS in biological reactions (21). Various exogenous stimulation, such as stress response, radiation, tumor radiotherapy, and chemotherapy, can also produce ROS (22). The endoplasmic reticulum (ER) can accompany ROS generation in the process of oxidative protein folding (23). Many antioxidant defense systems are launched to balance ROS and prevent excessive oxidative damage. These antioxidants can be divided into two categories:

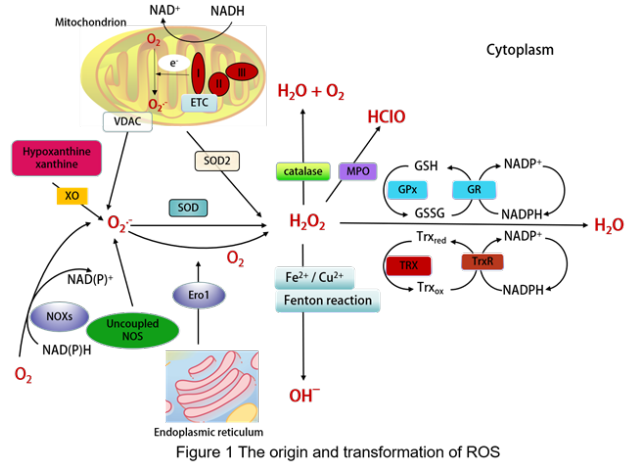

Figure 1 The origin and transformation of ROS

Figure 1. The origin and transformation of ROS.

nonenzymatic and enzymatic antioxidants. Nonenzymatic antioxidants such as flavonoids, glutathione (GSH), vitamins A, C, and E. Enzymatic antioxidants include SOD, glutathione peroxidase (GPx), gluathione reductase (GR), catalase (CAT), peroxiredoxin (PRX), thioredoxin reductase (TrxR), thioredoxin (TRX) and others. They can metabolize H_2O_2 to H_2O and O_2 (24). The cellular ROS content is in a state of dynamic equilibrium, which can maintain the stability of the body, so ROS will not cause harm to the body under physiological conditions. In addition, it is established that many transcription factors, including nuclear factor-kappa B (NF-κB), nuclear factor erythroid 2-related factor2 (Nrf2), the forkhead box protein O (FOXO) may be activated by ROS and further induce downstream genes to regulate intracellular redox environment (25).

Relationship of ROS in cancer

Biological oxidation is an important physiological process in the body; large amounts of ROS are released during this process resulting in human diseases including diabetes, inflammation, and cancer. Tumorigenesis is a gradual process that involves multistage reactions and the accumulation of gene mutations. A large number of studies have shown that the role of ROS in cancer may depend on several factors including tumor types, cancer stages, treatment strategies, duration of ROS, specificity, and ROS level (26). ROS has a dual effect on tumor cells. On the one hand, increasing ROS levels can accelerate the rate of cancer cell proliferation, activate growth factor signaling pathways via inhibiting phosphatases, and motivate a stress-responsive pathway that is resistant to chemotherapy (27). On the other hand, the high concentrations of ROS cause oxidative damage to proteins and nucleic acids, thereby leading to cancer cell death (28).

Cancer-promoting effect of ROS

During the process of tumorigenesis, a large number of genes, endogenous molecules, and pathways in cells first concentrate on transformation and promotion, and then manifest as cancer phenotype. And that most genes, molecules, and pathways involved in this process interact with ROS in cells, thereby promoting the evolution of cancer cells (29). Some genes can regulate the production of ROS to change the concentration of ROS. First, intracellular ROS can lead to the oxidation of lipids, proteins, and DNA damage, resulting in intracellular genomic instability, variation, and various cascades associated with tumorigenesis (30). Further, ROS can also stimulate various transcription factors to control tumor cell survival, proliferation and invasion, angiogenesis, and metastatic protein expression.

Related genes regulate the production of ROS

p53 gene with ROS. Wild-type p53 is a tumor suppressor protein that is important for cancer prevention. The results showed that loss of p53 function would increase ROS level and promote the growth of pancreatic cancer in mice (31). p53 regulates ROS by controlling the expression of certain enzymes that regulate ROS metabolism, thus adjusting the cells' redox capacity to inhibit tumor growth. NADPH increases GSH to decrease ROS levels, while p53 accelerates the pentose phosphate pathway to produce NADPH (32). p53 can also limit ROS levels by increasing thiol groups on the cell's surface and GSH and

SOD levels (33). They also upregulate the expression of glutathione peroxidase 1 (GPX1), and Nrf2, and maintain normal mitochondrial structures, thus limiting ROS production (34). Thus, when p53 is mutated, ROS levels are elevated and accelerate tumorigenesis.

K-Ras gene and ROS. K-Ras gene activates NADPH oxidase and generates ROS by promoting the binding of the NOXs component p47phox to the membrane component p22phox to induct tumorigenesis. CAT can block this pathway and inhibit tumorigenesis (35). Experiments have confirmed that the K-Ras gene promotes tumor cell production by activating NOXs to produce ROS (36). In addition, the activated K-Ras gene can upregulate miR-155 (miR-155, one of the best-characterized miRNAs) that the transcription factor forkhead box O3a (FOXO3a), which regulates superoxide dismutase 2 (SOD2) and CAT, lose their normal transcriptional activity, thereby promoting ROS production and inducing cell proliferation and transformation (37).

Sirtuin 3 (SIRT3) gene with ROS. SIRT3 is the most dominant deacetylating enzyme in the mitochondria, which regulates the acetylation level of key proteins in the mitochondria, maintaining mitochondria function and redox homeostasis (38). As a tumor suppressor gene, mice knocked out of SIRT3 could have breast tumors. It may be attributed to inhibiting the antioxidant activity and increasing the level of ROS (39). Finally, it causes mitochondrial DNA damage and develops tumors. SIRT3 can modulate manganese superoxide dismutase (MnSOD) and CAT by directly or indirectly deacetylating FOXO3a (40). It is also possible to regulate mitochondrial function and reduce ROS levels through pathways such as ETC and tricarboxylic acid circulation, thereby accelerating tumor progression (41). TP 53-induced glycolysis and apoptosis regulator gene (TIGAR) gene and ROS. TP 53-induced glycolysis and apoptosis regulator gene (TIGAR) regulates mitochondrial respiration and relates to the metabolism of tumors, which is the target gene of p53. Breast and lung cancer have a high level of GSH (42). TIGAR gene maintains the GSH level to decline the ROS concentration and inhibit the tumor cells. The deletion of the TIGAR gene may decrease ROS and inhibit the proliferation and survival of tumor cells (43).

ROS involved in the relevant signaling pathways

ROS is a second messenger for many signals, modifying the expression of tumor genes. Some common signal transduction pathways modulated by ROS include the mitogen-activated protein kinase (MAPK) signaling pathway, NF-κB signaling pathway, Keap1-Nrf2-ARE pathway, phosphoinositide-3-kinases (PI3K)/ AKT/ mammalian target of the rapamycin (mTOR) signaling pathway. Interleukin-6 (IL-6)/ signal transducer and activator of transcription 3 (STAT3) signaling pathway, CD44/GSH signaling pathway, and transcriptional activator protein-1 (AP-1) are also associated with ROS to control the tumor cells' proliferation and progression, thereby impacting tumor growth (44). Many studies have shown that some signaling pathways associated with ROS play an important role in tumorigenesis (45-47).

MAPK is a group of amino-threonine protein kinases that regulates gene expression via phosphorylating transcription factors and is generally involved in proliferation, differentiation, and apoptosis during the various stages of cancer occurrence. The signaling pathway MAPK is resistant to oxidation levels and directly affects the expression of cyclin D1 (an unstable specific cyclin in the G1 phase of the cell proliferation cycle). Since the expression of cyclin D1 has an oxidant-dependent effect, the transition period from G0 to G1 is the only phase in the cell proliferation cycle regulated by the redox signaling pathway (48). For example, in tumor cells, ROS involves in activates the MAPK/extracellular signal-regulated kinase (ERK) signaling, as a regulator of cell protection and proliferation to cope with oxidative stress and reduce apoptosis (49).

NF-κB signaling pathway can activate cellular genes for proliferation and apoptosis. NF-κB is a nuclear transcription factor, including growth factors, adhesion molecules, and cytokines. Activating NF-κB can cause proliferate and metastasize in cancer. Meanwhile, it is a redox-sensitive transcription factor; many proteins in the NF-κB signaling pathway can react with ROS. Like, NF-κB-induced kinase (NIK) activated by ROS phosphorylation, resulting in downstream IκB kinase complex (IKK) protein kinase integrating with NF-κB inhibitory kinase (IκB), eventually releasing NF-κB (50). In addition, the activation of NF-κB can be stopped by antioxidants.

Kelch-like ECH-Associating protein 1 (Keap1)-Nrf2-antioxidant response element (ARE) pathway is one of the most important defense mechanisms against oxidative and/or electrophilic stresses, and it is closely associated with inflammatory diseases, including cancer (51). Nrf2 is the important regulatory factor required for cells to maintain an oxidative steady state and is activated for under conditions of high oxidative stress (52). Nrf2 has a double effect on tumor growth. On the one hand, Nrf2 can defend the body away from carcinogenesis by activating the organism's reaction (53). It has been evidenced that the activated Nrf2 has a protective effect on premalignant lesions and suppresses the toxicity of aflatoxin (54). On the other hand, Excessive activation of Nrf2 in tumor cells cannot influence oxidative stress on tumor cells, thus causing an environment that promotes tumor cells growth (55). The activated Nrf2 leads to a decrease in ROS level, which mediates DNA oxidative damage and induces the invasion of tumor cells (56). Nrf2 promotes the expression of glutamate-cysteine ligase catalytic subunit (GCLC) and malic enzyme 1 (ME1) and improves the synthesis of GSH in tumor cells. As a reducing agent, GSH has an antioxidant function, which enhances tumor cells' antioxidant capacity and protects them from oxidative stress damage (57). A series of changes have shown that Nrf2 indirectly plays an important role in developing tumor cells by influencing ROS.

PI3K/AKT/mTOR signaling pathway is one of the most vital carcinogenic pathways in almost all cancers and has an essential effect on regulating cell survival, growth, apoptosis, and autophagy. H_2O_2 oxygenates the cysteine residue of the tumor suppressor gene phosphatase and tensin homolog protein (PTEN) and triggers the PI3K/AKT/mTOR signaling pathway (58). The inactivated PTEN gene activates NOXs. On the other hand, FOXO3a is phosphorylated, and phosphorylated FOXO3a can't be transcribed normally. Finally, the lack of FOXO3a suppresses the proliferation and transformation of cells (59). Moreover, glycogen synthase kinase-3β (GSK-3β) inhibits pyruvate dehydrogenase and α-ketoglutarate dehydrogenase complex, reducing ROS production. The activated

PI3K/AKT/mTOR signaling pathway promotes phosphorylation of GSK-3β, reducing its activity, and promoting the production of ROS (60). Consequently, PI3K/AKT/mTOR signaling pathway promotes the growth of cancer cells. Studies have shown that in the Brca1-deficient type of breast cancer, overexpressed PTEN inhibits the PI3K/AKT /mTOR signaling pathway. And it can decrease the ROS tolerance of cancer cells, and produce therapeutic effects (61).

The IL-6/STAT3 signaling pathway is involved in the development of tumors and the suppressors of cytokine signaling 3 (SOCS3) can suppress IL-6/STAT3, thereby inhibiting the growth of the tumor. The findings have suggested that the hepatitis B virus (HBV) generates ROS. ROS triggers IL-6/STAT3 signal transduction, in turn inhibiting the epithelial-mesenchymal transition (EMT) process induced by SOCS3 through the meditation Snail to SOCS3, which leads to inhibition of the growth and metastasis of tumor cells. Snail is a transcription factor of the zinc finger. The increasing Snail is positively correlated with the invasive ability of tumor cells (62).

CD44/GSH signaling pathway is closely related to tumors. CD44 is an adhesion molecule that reduces ROS primarily by interacting with the cystine/glutamate transporter xCT subunit of variant CD44. It also can increase the content of intracellular GSH, reducing the level of ROS to protect cancer stem cells against ROS damage (63), which promotes tumor proliferation, metastasis, and drug resistance. Moreover, the glycolytic enzyme pyruvate kinase M2 (PKM2) is a restriction enzyme during glycolysis, and experiments have shown that when its activity is inhibited, it can promote tumor formation (64). The decline in the activity of PKM2 promotes the production of NADPH and reduces ROS. CD44 can phosphorylate PKM2 to reduce its activity and promote the procession of glycolysis, which improves the antioxidant capacity of tumor cells (65).

AP-1 is the redox-sensitive transcription factor and is essential in cell proliferation and differentiation. It is a heterodimer composed of c-Fos (cellular-fos protooncogene) and c-Jun (cellular-jun protooncogene). Experiments have shown that ROS could stimulate AP-1 by activating extracellular regulated protein kinases 1 (ERK1) and extracellular signal-regulated kinase 2 (ERK2) in the MAPK family (66). Some experiments confirmed that subcloning breast cancer cells are formed after stimulating breast cancer cells (MCF7 cells line) with chemical drugs; among these cells, the ROS production rate, cell motility, and aggressiveness in the new cells have significantly increased. During this process, CXCL14 (chemokine ligand 14), plays an important role in the upregulation of expression. The subcloning of breast cancer cells have high level of ROS, and it can lead to increased activation and binding of the AP-1 transcription factor to the CXCL14 promoter, thus inducing its expression (67).

Cancer-suppressing effect of ROS

Necrosis

Massive levels of ROS may cause necrotic cell death, including necroptosis. Necrosis is caused by various pathogenic factors that disrupt or stop the normal metabolic activities of cells and kill the cells. Necrosis is usually accompanied by the mitochondrial membrane potential (ΔΨm) and ATP level declining. Previous reports have described that mitochondrial ROS promotes cancer cell necrosis (68). In a study, chrysophanol produced ROS in A549 cells, ΔΨm and ATP level remain significantly lower and it has been shown that chrysophanol induces lung cancer cell death through initiating necrosis (69).

Apoptosis

Apoptosis means the spontaneous death of gene-controlled cells to keep the environment safe. Apoptosis, as a strictly controlled form of cell death, can be initiated by an intrinsic pathway such as mitochondria or by an extrinsic pathway such as a death receptor. ROS-driven oxidative stress-induced apoptosis is of great concern (70). ROS activates death receptors in tumor cells through exogenous pathways, which facilitate apoptosis. Quercetin has apoptosis by upregulating the expression of ROS (71). The endogenous pathway apoptosis is mainly the release of cytochrome C through mitochondria, thereby of caspase family proteins. ROS can regulate the mitochondrial cell apoptosis pathway and the p53, and the NF-κB pathway (72). The Bcl-2 family is one of the important signaling proteins family that regulates apoptosis (73). In addition, it has been reported that pyruvate kinase M2 isoform in mitochondria could regulate oxidative stress-induced apoptosis through stabilizing antiapoptotic members of B-cell lymphoma 2 (Bcl2) (74). Recent studies show that ROS can also induce apoptosis of tumor cells through multiple signaling pathways (75). High levels of ROS stimulate the p38 MAPK pathway and narrow the lifespan of hematopoietic stem cells (76). ROS activates the p38 MAPK pathway by modulating FOXO3 and Bmi1 protein, thus blocking the growth of glioma cell stem cells (77, 78). ROS induces senescence and death in cells by activating the apoptosis signal-regulating kinase 1 (ASK1)/c-Jun N-terminal kinase (JNK) signaling pathway. H_2O_2 oxidizes TRX1 and activates ASK1, thereby activating the JNK and p38 MAPK pathways, inhibiting anti-apoptotic factors and promoting apoptosis (79). In mouse B lymphoma cells, membrane immunoglobulins induce H_2O_2 to activate the ASK1/JNK pathway to lead to apoptosis (80).

Autophagy

Autophagy is a normal phenomenon that protects normal cells and removes abnormal cells. The autophagy procession is the phagocytosis of cytoplasmic or organelles and encapsulation of vesicles, fusing with lysosomes to form the autophagosomes. Autophagosomes degrade the contents of cells to meet the metabolic needs of the cells and organism (81). To balance the normal body's internal environment homeostasis, excess ROS will activate the apoptosis pathway and stimulate autophagic cell death. Autophagy caused by ROS has two effects on the cell itself. First, ROS through the self-protecting agent relieves oxidative stress; on the other hand, ROS stimulates autophagy cell death and has a devastating effect on the cell's immune system (82). Autophagy is associated with the production of intracellular ROS, and mice are strongly stimulated to trigger apoptosis and cause autophagy response, in which autophagy and apoptosis have been coordinated together (83). ROS can reduce the proliferation of melanoma cells by activating autophagy (84). Oxidative stress caused by H_2O_2 and 2-methoxyestradiol (2-ME) leads to the death of cancer cell lines U87 and HeLa cells through autophagy. To inhibit or knockout the autophagy gene of oxidative

stress-induced cell death can effectively prevent cell death. In addition, N-Acetyl-L-cysteine (NAC) can induce ROS production to autophagy and cell death (85).

Ferroptosis

Ferroptosis is a recently recognized form of regulated cell death (RCD), which is characterized as iron-dependent and caspase-independent nonapoptotic cell death (86). Numerous evidence suggest that the following proteins and signaling pathways are involved in ferroptosis, such as involvement of NOX enzymes (especially NOX1), depletion of intracellular GSH, suppression of cystine uptake, inhibition of GPx4, and induction of lipid peroxide formation (87).

In summary, ROS has a dual role in cancer. The concentration of intracellular ROS is accompanied by the entire process of cancer development. As shown in Figure 2, as the level of intracellular ROS increases, it will contribute to the biochemical changes necessary for tumor initiation, promotion, progression, invasion and metastasis. If a higher level of ROS continues to be escalated to a threshold, the level of toxicity, it will provide a pathway for cancer treatment by enhancing activation of various cell death pathways such as apoptosis, necrosis, autophagy, and ferroptosis.

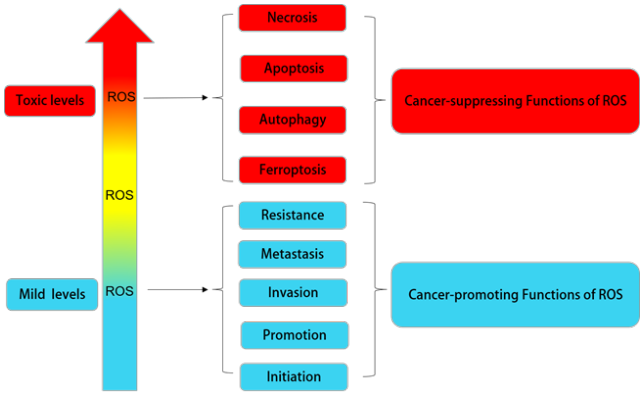

Figure 2 Dual effects of ROS on tumor cells

Figure 2. Dual effects of ROS on tumor cells.

ROS-related Natural compounds

As described in the dual effects of ROS on cancer, it seemingly provided therapeutic strategies to prevent or treat cancer. The first strategy is to prevent and reduce intracellular ROS levels by suppressing ROS production or enhancing antioxidants to remove the ROS. The second strategy is to improve the ROS levels to toxicity to activate ROS-induced cell death pathways. According to current research, the most effective method is to exploit small molecules that increase ROS or inhibit the antioxidant systems. We summarized the 8 natural compounds from the polyphenols, flavonoids, alkaloids, saponins, and terpenoids compounds (see Table 1). They have the stronger anticancer activity and some of them are promising options for cancer treatment.

Proanthocyanidins

Proanthocyanidins (PAs), also known as condensed tannins, are a class of polymers formed by the condensation of different amounts of catechins or epitechins. PAs are widespread in plants and in food of plant origin, in particular in fruits, legume seeds cereal grains and different beverages. PAs have pharmacological activities such as antioxidant, anti-myocardial ischemia-reperfusion damage, anti-atherosclerosis, protection of vascular endothelial cells, and anticancer. Studies have found that proanthocyanidins B2 can cause apoptosis and autophagy in rectal cancer cells through downregulating p-PI3K, p-AKT, and p-mTOR proteins in the PI3K/AKT/mTOR pathway (88-90). PAs in the cinnamon extract can inhibit the activity and expression of Nrf2 in non-small cell lung cancer (NSCLC) A549 cells (91). In A549 cells overexpressed in Nrf2, PAs can selectively decrease the mRNA level of Nrf2, thereby stimulating massive intracellular ROS production and inhibiting tumor cell proliferation (92). Epigallocatechin-3-gallate (EGCG) is capable of restoring the enzymatic activity of glutathione peroxidase and can regulate glutathione levels. Through its antioxidant properties, EGCG exhibited a protective effect against DNA damage. And many studies have confirmed Proanthocyanidins effect in human clinical trials (93).

Ginsenoside

Ginsenoside (GS), is one of the major active components of Panax ginseng (94). It has multiple pharmacological actions and has been using for treatments of cancer, obesity, diabetes, and cardiovascular diseases (95). Ginsenoside mainly exerts anti-tumor effects by regulating the tumor cell cycle, influencing tumor signaling, influencing tumor tissue angiogenesis, and inducing apoptosis. Studies have confirmed that ginsenoside-Rg2 (G-Rg2) in breast cancer MCF-7 cells activate the transcription factors in the AMP-activated protein kinase (AMPK) pathway. Then, generating a high concentration of ROS to cause the MCF-7 cells to apoptosis (96). It can also induce mitochondrial damage by reducing membrane potentials to decrease the level of ROS, which further inhibits the growth of tumors

Table 1. Natural compounds with ROS anticancer activity.

Category	Natural compounds	Main Source	References
1	Proanthocyanidins (PAs)	Grape seeds	88-93
2	Ginsenoside (GS)	Panax ginseng	94-101
3	Betulinic acid (BA)	Birch tree	102-106
4	Luteolin (LUT)	Reseda odorata	107-115
5	Curcumin	Curcuma Rhizome	116-122
6	Piperlongumine (PL)	Piperine	123-129
7	Berberine	Coptidis Rhizoma	130-139
8	Parthenolide (PTL)	Tanacetum balsamita	140-149

(97). Ginsenoside-Rh2 stimulates mitochondrial ROS production by targeting the mitochondrial ETC complex, thereby promoting apoptosis of cervical cancer cells (98). Ginsenoside-Rg3 (G-Rg3) activates the release of mitochondrial cytochrome C, activates the caspase-3 and Bax protein, and inhibits the synthesis of Bcl-2 protein and the form of ROS within cells, causing apoptosis of liver cancer (99). Ginsenoside-Rh4 (G-Rh4) increases the accumulation of ROS in colon cancer and subsequently activates the JNK-p53 pathway to induce autophagy, leading to apoptosis (100). One study in NSCLC, G-Rg3 combined with chemotherapy could better improve the object response rate (ORR) (101,102).

Betulinic acid

Betulinic acid (BA), a compound of the five-ring trichoctoric mushroom, has been successfully extracted from birch bark. It was found in a variety of traditional Chinese medicines such as white peony, jujube, eucommia, licorice, and sour jujube kernel. BA has a wide range of sources and good therapeutic effects, that are used for treatments of cancer and infection (103). In the melanoma study, we found that BA has no effect on the physiological function of normal cells, and targets induction of tumor cell apoptosis (104). Studies of human oral squamous cell carcinoma found that BA activates the p53 signal by regulating ROS, significantly increasing ROS, regulating cell cycle, and therefore regulating tumor cell growth (105). BA downregulates the Bcl-2 gene and upregulates the Bax gene to induce apoptosis in cervical cancer cells through the endoplasmic reticulum pathway and ROS-mediated mitochondrial pathways (106).

Luteolin

Luteolin (LUT) is a flavonoid compound widely in vegetables, fruits, flowers, spices, and medicinal plants. LUT effectively modifies glycolipid metabolism, prevents cardiovascular disease, and has various pharmacological effects such as antioxidants, anti-inflammatory, and antitumor (107). It copes with oxidative damage to tissues and cells by increasing the level of antioxidant enzymes in the body and reducing the production of ROS. In breast and colorectal cancers, LUT promotes the apoptosis protein Bax and cleaved-caspase3 and cleaved-poly-ADP-ribose polymerase (PARP). Cleaved-caspase3 and cleaved-PARP are the major substrates of both caspases, is a valuable markers of apoptosis. The caspase signal was finally activated to initiate apoptosis (108-110). LUT reduces intracellular ROS and induces apoptosis of melanoma cells by inhibiting PI3K/AKT signaling (111). It also decreases the expression of Nrf2 and mRNA protein, leading to the downregulation of the antioxidant-response element (ARE) driven genes, improving the sensitivity of A549 cells to oxaliplatin, bleomycin, and doxorubicin (112). Similarly, in HepG2 hepatocarcinoma cells, luteolin caused induction of cell death and reduction of tumor in a xenograft model. It also suppressed the NF-κB DNA-binding activity and caused the release of ROS; these intracellular ROS in turn mediate AMPK-NF-κB signaling (113). A group of researchers found that the combined treatment of LUT and celecoxib has synergistic effects through Akt inactivation and ERK signaling inhibition in MCF-7 cells (114). Similarly, treatment of human breast cancer MDA-MB-231 cells with luteolin and paclitaxel activated the caspase-8, caspase-3 and enhanced the expression of Fas ligand. Finally, the tumor size and weight are both turn small than before (115).

Curcumin

Curcumin is an organic compound extracted from Curcuma Rhizome. It has many medicinal effects, including anti-inflammatory, antioxidant, anticoagulant, hypolipidemic, anti-arteriosclerosis, and anti-tumor effect (116). Curcumin has a potential anti-tumor effect, which can inhibit the transformation, proliferation, metastasis, and angiogenesis of tumors, even increase the sensitivity of tumor cells to chemotherapy drugs and induce apoptosis. Curcumin declines the level of ROS in cells, thus inhibiting the production of lipid peroxide Malondialdehyde (MDA). Curcumin hinders cancer development in the presence of ROS. It inhibits the proliferation of glioblastoma and liver cancer stem cells by ROS-mediated activation of the MAPK pathway, which downregulates of STAT3 activity, suppression of NF-κB signaling, and IAP family members (117, 118). In human gastric cancer, curcumin has been proven to induce the generation of ROS in BGC-823 cells and apoptosis via ROS-mediated ASK1-MAPK kinase 4 (MKK4)-JNK signaling pathway (119). It has been demonstrated that curcumin causes oxidative stress by inducing ROS burst, decreasing glutathione, and wrecking mitochondria membrane potential (MMP), which was reversed by NAC (120). The research found that 25 pancreatic cancer patients with 8g/d curcumin for 8 weeks. One patient had a brief, but marked, tumor regression(73%). Curcumin inhibition in the growth of cancer may be related to the down-regulated expression of NF-B signal transducer (121). Curcumin can reduce glutathione S-transferase (GST) in human colorectal cancer. Further, it reduces the antioxidants GSH to increase the intracellular ROS in order to inhibit the process of cancer(122).

Piperlongumine

Piperlongumine (PL) is an alkaloid extracted from the traditional Chinese medicine piperine. It effects on anti-inflammatory, anxiolytic, antiplatelet, antibacterial, and antitumors (123). Experiments have proved that PL inhibits tumor cells through different signaling pathways, such as gastric cancer, cholangiocarcinoma, lung cancer, and breast cancer (124-126). PL raises ROS in the abnormal metabolism of MG63 cells, putting them into a state of oxidative stress, causing mitochondrial damage, and regulating the ROS/PI3K/AKT signaling pathway to activate caspase-9. Further, the mitochondrial death pathway activates caspase-3 thereby triggering apoptosis. Finally, it stagnates the cell cycle in the G2/M phase, producing potent anti-tumor (127). It has been demonstrated that PL generates primary myeloid leukemia cell apoptosis and autophagic death by activating ROS (128). For example, Oxaliplatin and PL can work together to induce apoptosis of colorectal cancer cells. Since ROS is the interplay between PL and Oxaliplatin, ROS facilitates the regulation of endoplasmic reticulum stress, inhibits tumor cell migration, and promotes apoptosis (129).

Berberine

Berberine is a low-toxicity natural isoquinoline alkaloid, found in various medicinal plants such as Coptidis Rhizoma and Cortex Phellodendron, and has good anti-

infection, hypoglycemic, lipid-lowering, and antitumors effects (130). Previous studies on berberine have found that it has therapeutic effects on many tumors, including osteosarcoma, prostate cancer, and liver cancer (131, 132). Berberine can reduce cancer cell growth activity and promote apoptosis of cancer cells via signaling pathways, interfering with the growth cycle of cells (133, 134). Berberine downregulates the inflammatory factors and reduces the degree of intracellular oxidative stress. Further, it regulates microRNA controls cellular signaling pathways, and causes apoptosis of rectal cancer cells (135). Research has observed that the ammonia nitrogen of berberine penetrates the penetration of biofilms, allowing the drug to accumulate in organelles, especially in mitochondria. The high concentration of berberine in cells inhibits the activity of NADH oxidase and succinate dehydrogenase, which hinders the mitochondrial respiratory chain. It can result in cellular oxygen utilization disorder, and a large number of $O_2^{\bullet-}$, $OH^{\bullet}$, remain to be generated and accumulated, causing mitochondrial damage (136). Studies have shown that berberine induces a large amount of ROS in MCF-7 cells of breast cancer, which damages mitochondrial function and decreases $\Delta\Psi m$. Finally, berberine induces apoptosis and subsequently exerts an antitumor effect (137). Berberine causes mitochondrial dysfunction and induces autophagy death of hepatocellular carcinoma cells by down-regulating the PI3K/AKT/mTOR signaling pathway and upregulating ROS-mediated Hep3B cells (138). In a multicenter, doubt-blinded, randomized controlled study in colorectal adenoma. Using 0.3g berberine twice a day can reduce the risk of recurrence of colorectal adenoma and as an option for chemoprevention after polypectomy (139).

Parthenolide

Parthenolide (PTL) is the main effective ingredient in the herbaceous plant Tanacetum balsamita. Previous studies have confirmed that PTL has various pharmacological effects, including anti-inflammatory immunosuppressive effects, antioxidants, antitumors, and inhibition of expression of NF-κB (140). PTL inhibits the growth of tumor cells such as breast cancer, prostate cancer, leukemia, lung cancer, stomach cancer, colon cancer, and kidney cancer (141-143). It promotes oxidative stress by activating NOXs and inhibiting the intracellular antioxidant enzyme system. In prostate cancer cell research, PTL induces the activation of NOXs in PC-3 cells to generate ROS and induce oxidative stress, thereby exerting antitumor cell effects (144). PTL can induce the HepG2 cells of human hepatocellular carcinoma cells to generate ROS, intercept the cell cycle, and cause autophagy and apoptosis. PTL can cause BGC-823 cells of stomach cancer to produce more ROS, causing G1 phase blocking and apoptosis. Meanwhile, PTL induces autophagy of human osteosarcoma cells through a ROS-dependent pathway (145). It also acts via NF-κB to inhibit the cancer. Oxidative stress may also contribute to the effects of parthenolide. Parthenolide-induced apoptosis is preceded by a decrease of the levels of intracellular thiols, including both free GSH and generation of ROS (146). PTL and other naturally derived agents (curcumin, betulin, withanolides, lactoferrin) when administered with the standard platinum and etoposide treatments lead to a complete regression of advanced small lung cell carcinoma and the patient remains in full remission for more than 7 years (147).

Conclusion

This review will help better understand the relationship between natural compounds associated with ROS and malignancies in chemoprevention, anticancer mechanisms, and treatment. These compounds modulate various signaling pathways to promote apoptosis and autophagy, stop cell cycles, and inhibit the growth of tumor cells. These natural compounds can be combined with other anti-tumor treatments to enhance anticancer effects and reduce side effects. ROS is a double-edged sword because the different concentrations and other conditions have different biological effects. A low concentration of ROS promotes cell division, but a high concentration of ROS induces apoptosis of tumor cells. In addition, ROS function is complicated, including a variety of signaling pathways and physiological functions. In regulating ROS in anti-tumor drugs, the relevant information in the body should be monitored during the treatment process to ensure the anti-tumor effect of ROS. Even so, ROS-related drugs still play an important role in the development and treatment of malignancies. Therefore, inducing tumor apoptosis by regulating intracellular ROS levels remains a primary antitumor strategy. In summary, with expanding knowledge of ROS functions, chemoprevention of tumorigenesis and chemotherapeutic interventions of tumor development by regulating ROS homeostasis are now becoming possible and are entering clinical trials, highlighting the bright future of ROS-mediated cancer therapy.

Conflict of Interests

The authors declared no conflict of interest.

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