Prospective Application of Natural and Synthetic Redox Modulators in Oxidative Stress-Targeted Cancer Therapy

121

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Contents

Abstract

While recognizing the differences in the pathogenesis of different malignancies, the outstanding body of evidence has been accumulated in the past few decades, implicating the role of oxidative stress in the process of cancer initiation and progression. Cancer cells exhibit an altered energy metabolism and highly efficient redox systems that enable rapid cell proliferation and survival in various conditions. The adaptation/resistance of cancer cells to chronic oxidative stress through different mechanisms usually leads to drug resistance. The specific disruption of the redox capacity with either scavenging the excessive intracellular ROS or inducing ROS generation through exogenous oxidative insult represents a promising approach for cancer therapy. A considerable research effort has been dedicated to identifying the therapeutic agents with redox-modulation capacity that may impede cancer. Based on the established knowledge in these subjects, the natural and synthetic redox modulators currently used or under investigation for their potential application in the oxidative stress-targeted cancer therapy are reviewed.

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Keywords

Oxidative stress · Redox modulators · Cancer therapy · ROS-depleting strategy · ROS-elevating strategy

Introduction

The outstanding body of evidence has been accumulated in the past 50 years, implicating the oxidative stress in broad-ranging pathologies, including mitochondrial diseases, aging-related diseases, neurological diseases, cancer, autoimmune diseases, and some genetic disorders (Lazarevic-Pasti et al. 2017). Current concepts in redox biology and medicine emphasize the significance of metabolism and redox dysregulation in cancer. A characteristic feature of most tumors is hypoxia, which leads to an altered redox signaling affecting metabolism, proliferation, apoptosis, as well as angiogenesis (Farhood et al. 2019). As comprehensively reviewed by Sosa et al., ROS promote many biological processes involved in tumor development and progression such as cellular proliferation, avoidance of apoptosis or anoikis, tissue invasion and metastasis, and angiogenesis (Sosa et al. 2013). The NOX, COX, LOX, and NOS are the key enzymes generating ROS/RNS that act as redox messengers and trigger the activation/inhibition of signal transduction kinases/phosphatases, such as the protein tyrosine kinases and protein tyrosine phosphatases. These interactions, in turn, activate downstream signaling pathways, including protein kinase of the MAPK cascade, PI3K, and PKC. Several biochemical pathways related to cellular proliferation, which involve key signaling proteins such as Nrf2, Keap1, Ras, Raf, MAPK such as ERK1/2, MEK, p38α, c-Jun N-terminal kinase (JNK), c-myc, p53, and PKC, could be affected by oxidative stress (Sosa et al. 2013). The metabolic and redox signaling pathways are closely interrelated with cell proliferation and apoptotic regulatory pathways. Generally, an accelerated metabolism of cancer cells is associated with an impaired antioxidant defense system (ADS) and persistently high levels of ROS (Fig. 1); however, some cancer cells die when ROS levels are elevated. Therefore, there is still considerable controversy as to whether ROS manipulation therapy by ROS- elevation or ROS-elimination is beneficial for the treatment of cancer.

Both pro- or antioxidant therapies have been recommended, and multiple approaches have been evaluated for the targeting of metabolic alterations, ROS signaling pathways, and redox mechanisms involved in cancer initiation and progression. Accordingly, several drugs and compounds have been proposed as a promising strategy for treating cancer.

An overview of the ROS-manipulation strategies, including natural and synthetic compounds that are considered efficient in modulating redox capacity in cancer cells, is presented.

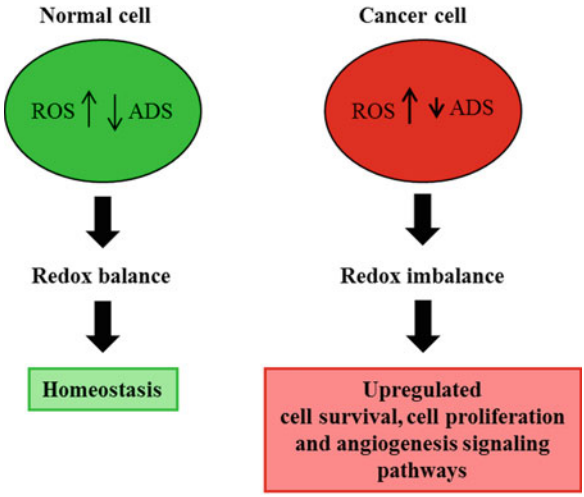

Fig. 1 Redox status of normal and cancer cell

ROS-Manipulation Strategies in Cancer Treatment

A disruption of the redox balance in the tumor by activation of both oxidative and antioxidative mechanisms represents a promising therapeutic approach (Fig. 2). In other words, cancer-targeted therapies can be performed by overloading cancer cells with either antioxidants or prooxidants (Farhood et al. 2019).

ROS-Depleting Strategy in Cancer Treatment

The antioxidant overload in cancer cells could be achieved through exogenous administration of antioxidant molecules and/or inhibitors of oxidative stress inducers such as COX-2, nitric oxide synthase, and NOX system. One such agent is hormone melatonin, which is one of the most promising antioxidant agents for cancer therapy. Melatonin is proved to efficiently scavenge free radicals, stimulate antioxidant enzymes, and inhibit prooxidant enzymes (Farhood et al. 2019). The enhancement of ROS scavenging enzymes is one of the strategies aimed to combat cancer, which is supported by studies that overexpression of superoxide dismutase (SOD), catalase, or glutathione peroxidase inhibits cancer cells growth (Wang and Yi 2008). Promising results were obtained via targeted delivery of PEGylated catalase or SOD to metastatic tumors (Wang and Yi 2008). Besides studies on the combined use of mitochondrial nutrients with conventional antioxidants, there is a substantial interest in the use of natural compounds as antitumor agents that can be used in cancer

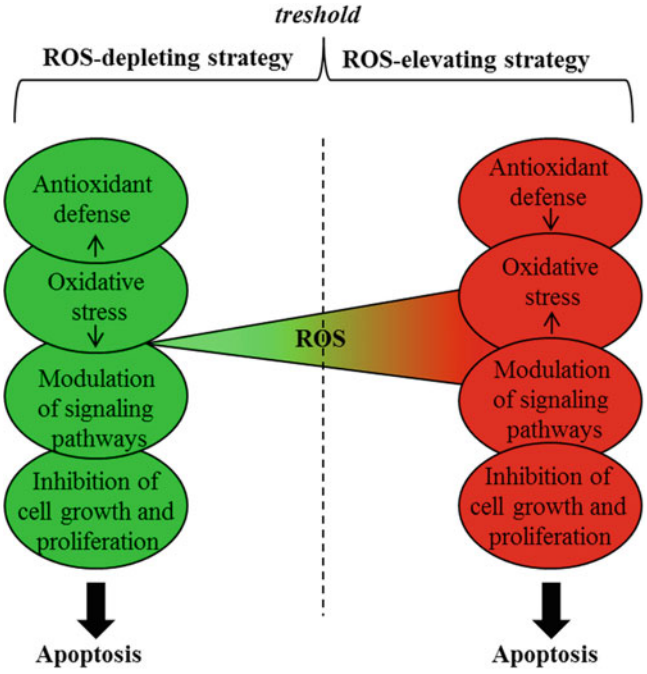

Fig. 2 Cancer treatment via modulation of the redox status in cancer cells

prevention and treatment, either alone or in combination with chemotherapy/radiotherapy. According to the antioxidant hypothesis, the high content of antioxidant molecules found in medicinal plants could directly mitigate the oxidative stress-induced complications of various pathologic conditions (Leskovac et al. 2013).

It is well established that the Mediterranean diet, which is characterized by high antioxidant content may be useful in delaying or preventing tumor development. Several traditionally used plants such as cruciferous vegetables, tomatoes, garlic, turmeric, coriander, cumin, ginger, green tea, mint, oregano, etc., have been identified by the National Cancer Institute as possessing cancer-preventive properties (Sobha and Andallu 2013). Polyphenols and carotenoids are the two main groups of antioxidant phytochemicals that contribute the most to the antioxidant properties of foods. The mechanisms underlying antioxidant activities of natural compounds include, but are not limited to, the radical scavenging, metal chelation, inhibition of oxidases, regeneration of endogenous antioxidants, and activation of antioxidant enzymes.

During the cancer chemopreventive drug discovery, one of the most important findings was the stilbene **resveratrol** found in blueberries, cranberries, nuts, red grapes, and wine (Pezzuto 2019). It is reported that resveratrol mediates inhibition of cyclooxygenase (COX)-1, reduces intracellular ROS level, and suppresses cancer cell glycolytic metabolism in a wide range of cancers including breast, colorectal, liver, pancreatic, prostate cancer, and lung carcinoma (Mileo and Miccadei 2016;

Iqbal et al. 2017). In addition, resveratrol is found to induce phase II drug-metabolizing enzymes and inhibit cyclooxygenase and hydroperoxidase functions in human promyelocytic leukemia (Wang et al. 2012). It is shown that resveratrol exerts an antioxidant effect with a reduction of H_2O_2 and lipid peroxidation in the skin (Pezzuto 2019). Resveratrol is reported to inhibit metastasis in colon cancer cells by reducing hypoxia inducible factor-1α and MMP-9 expression, and to inhibit Wnt signaling and beta-catenin localization in colon-derived cells (Wang et al. 2012).

Nonetheless, depending on the applied concentration, time of exposure, and the cell type, it is also proposed that resveratrol can exhibit cytotoxic and prooxidant effects (Mileo and Miccadei 2016). Among many natural compounds tested for chemoprevention activity, **curcumin**, a flavonoid extracted from the Indian turmeric spice (*Curcuma longa*), has drawn special attention because of its antiproliferative, antioxidant, and carcinogen blocking effects (Sobha and Andallu 2013; Park et al. 2013). Curcumin is demonstrated to induce ROS scavenging enzymes, but on the other hand, it also displays prooxidant effects at high concentrations (Park et al. 2013). Antitumor activity of curcumin is linked to its ability to induce the expression of phase II drug-metabolizing enzymes (glutathione-S-transferase and quinine reductase) and ROS scavenging enzyme – hemeoxygenase-1 via activation of Nrf2 signaling, restoration of tumor suppressor p53, and modulation of inflammatory mediators like TGF-β and COX-2, which implicated its antioxidant and anti-inflammatory effects (Mileo and Miccadei 2016). Besides, in patients with precancerous conditions such as oral leukoplakia and oral submucous fibrosis, curcumin is found to decrease serum levels of malondialdehyde and 8-hydroxydeoxyguanosine and to enhance levels of antioxidants (vitamins C and E) (Park et al. 2013).

It should be noted that curcumin is characterized by poor bioavailability due to the β-diketone moiety that is responsible for the instability and weak pharmacokinetic profile of curcumin (Park et al. 2013). Its metabolites, particularly hydrocurcumins are considered more potent antioxidants than parent curcumin in scavenging free radicals, reducing lipid peroxidation, and in antioxidant enzyme activation. As comprehensively discussed by Park et al., a series of curcumin analogs with increased water solubility and improved pharmacokinetic properties have been synthesized, some of them being at least ten-fold more potent than natural curcumin (Park et al. 2013).

Just like curcumin, **quercetin** has also received considerable attention over the past decade. Quercetin is a polyphenolic flavonoid abundantly present in kales, onions, berries, apples, red grapes, broccoli, cherries, as well as tea and red wine (Xu et al. 2019). It is found that quercetin prevents cancer by modulating cell signaling pathways, oxidative stress markers such as lipid peroxides and H_2O_2, and by increasing antioxidant enzyme levels (Rauf et al. 2018). The anticancer effects of quercetin are reported in lung, prostate, liver, breast, colon, and cervical cancers (Rauf et al. 2018). Due to low bioavailability, several studies have been carried out to modify the structure of quercetin in order to enhance its performances. As extensively discussed by Xu et al. (2019), combining quercetin with metal ions

such as vanadium, copper, magnesium, iron, ruthenium, cobalt and cadmium, calcium, and rare earth elements significantly enhances its free radical scavenging and total antioxidant activities compared to those of pure quercetin. Similar results were obtained when applying the complexes of quercetin with complex ions (glucan–quercetin conjugate, calcium phosphate–quercetin nanocomplex (CPQN), and quercetin–germanium nanoparticles) (Xu et al. 2019). The promising results in the treatment of hepatocellular carcinoma were achieved when a combination of maleic acid and quercetin was applied. It is shown that this combination of a prooxidant/antioxidant had a cytotoxic effect on HuH7 and HepG2 liver cancer cells, but not on normal human epithelial cell lines (Carrasco-Torres et al. 2017). Furthermore, the combination of resveratrol and quercetin in subapoptotic doses is suggested to be a proper candidate treatment for glioma tumors (Mileo and Miccadei 2016).

Cyanidin, a flavonoid isolated from apples, grapes, plums, blackberry, raspberry, red berries, cranberry, red onion, and red cabbage is reported to possess antioxidant and radical scavenging effects, and to inhibit cell growth and division through modulation of COX-2 and iNOS gene expression in colon cancer cells (Iqbal et al. 2017). Cyanidin-3-O-glucoside, cyanidin-3-O-rutinoside, and the ethanol extract of freeze-dried black raspberries are found to induce significant growth inhibition and induction of apoptosis in a tumorigenic rat esophagus cell line (RE-149 DHD) (Wang et al. 2012). As reviewed by Iqbal et al., the cyanidin glycosides from red berries stop the synthesis of COX-2 enzyme in colon cancer, induce apoptosis in prostate cancer, stop MMP-9 expression in bladder and lung cancer, stop the Erk phosphorylation and MMP-2 in fibrosarcoma cells, and suppress expressions of JNK, MMP-9, and Erk enzymes in gastric cancer (Iqbal et al. 2017). Similarly, **kaempferol**, a major flavonoid aglycone from the *Kaempferia* (Zingiberaceae) rhizome, is also reported to downregulate the COX-2 gene expression and subsequent gene products related with cancer (Zhang et al. 2015). Wang et al. recently demonstrated the potent free radical scavenging activity of kaempferol and its ability to decrease superoxide anion, hydroxyl radical, and peroxynitrite levels to inhibit AKT phosphorylation and to cleave caspase-9, caspase-7, caspase-3 and PARP in human hepatoma cell line HepG2 cells (Wang et al. 2018b).

Fisetin, a flavone from plants such as *Acacia greggii*, *Acacia berlandieri*, strawberries, apple, persimmon, grape, onion, and cucumber, is considered a potent antioxidant, which modulates protein kinase and lipid kinase pathways (Wang et al. 2012). Fisetin is found to influence cell signaling pathways in various human tumors, including non-small cell lung cancer (Wang et al. 2012). Along with other flavonoids such as luteolin and quercetin, fisetin is reported to induce the expression of Nrf2 and the phase II gene product HO-1 in human retinal pigment epithelial cells, which protects them from oxidative stress-induced cell death (Wang et al. 2012). **Wogonin**, one of the flavonoids isolated from a Chinese medicinal herb *Scutellaria baicalensis* Georgi (Huangqin) showed broad toxicity against various types of tumor cell lines owing to its ability to inhibit nitric oxide, pro-inflammatory cytokines, and to reduce the expression of COX-2 (Sobha and Andallu 2013). Numerous studies have reported that isoflavones are beneficial for human health owing to their antioxidant activity. Among them, **genistein** found in soybeans, fava beans,

kudzu, *Fleminga vestita*, and coffee, has gained the most attention (Mileo and Miccadei 2016). Genistein is reported to act as a chemopreventive agent against several types of cancers, particularly hormone-dependent breast cancer, most likely by inhibiting the enzymes that regulate cell division and cell survival. In the breast cancer cell lines, genistein is shown to bind estrogen receptors, which consequently influence the cell proliferation rate, oxidative stress regulation, mitochondrial functioning, and antioxidant enzymes activities (Mileo and Miccadei 2016; Wang et al. 2012; Iqbal et al. 2017).

Several studies have shown the anticancer potential of terpenoids that are traditionally used for medicinal purposes. Recently, the monoterpenoid **cannabigerol**, from *Cannabis sativa*, is indicated as a potential cytoprotective agent, which is gaining attention for its antioxidant capabilities. Cannabigerol is reported to induce a SOD overexpression (Vallejo et al. 2017).

Among traditionally used terpenoids, carotenoids have been widely explored as anticancer agents. **Lycopene**, a carotenoid from red fruits and vegetables like tomatoes, carrots, watermelons, papayas, etc., has strong antioxidant properties, and its anticancer effects mainly attributed to induction of phase II drug-metabolizing enzymes have been reported in many studies, especially on prostate cancer, breast and endometrial cancer, and colon cancer (Wang et al. 2012; Bilecova-Rabajdova et al. 2013). **Crocetin**, the most potent carotenoid in saffron, has been listed as a potent anticancer agent against human lung cancer, colorectal cancer, breast cancer, and skin carcinoma (Wang et al. 2012). It is suggested that crocetin affects cancer cells by strengthening antioxidant defense systems, inhibiting nucleic acid synthesis, inducing apoptosis, and impeding growth factor signaling pathways (Wang et al. 2012). It is also found that saffron extract may have synergistic effects when combined with synthetic compounds, sodium selenite, or sodium arsenite, which may further improve cancer chemoprevention (Sobha and Andallu 2013).

Phenol acids and their derivatives have also been widely used in cancer treatment research due to their antioxidant effects. For example, **ellagic acid**, a polyphenolic antioxidant found in raspberries, strawberries, and cranberries, demonstrates chemopreventive effects by limiting oxidative stress (Bilecova-Rabajdova et al. 2013). On the other hand, caffeic acid found in coffee, potatoes, apples, and pears has demonstrated anticancer activity by increasing the ROS production (Vallejo et al. 2017). **Rosmarinic acid**, a caffeic acid ester from rosemary, is a natural antioxidant reported to show anticancer activities against several human cancers such as colon carcinoma cells, breast carcinoma, leukemia, etc. In human leukemia U938 cells, rosmarinic acid significantly sensitized TNF-α-induced apoptosis through the suppression of NF-κB and reactive oxygen species. It suppressed NF-κB activation through inhibition of phosphorylation and degradation of IκBα (Wang et al. 2012). **Chlorogenic acid**, another ester of caffeic acid, is also found to protect against carcinogenesis by the upregulation of phase II enzymes and suppression of ROS-mediated NF-κB, AP-1, and MAPK activation (Sobha and Andallu 2013).

Among plant oils, volatile oil from **ginger** has been reported as a promising therapeutic agent against melanoma. It inhibits cell proliferation and melanogenesis of murine B16 cells due to various alkene-containing substances (zingiberene and

iso-horn teaene), which scavenge ROS and inhibit lipid peroxidation. This oil is also found to suppress melanin synthesis and to upregulate the SOD, GSH, and catalase levels in B16 cells (Wang et al. 2018c).

Anticancer activities have been reported for cruciferous vegetables that are rich in phytochemicals that deplete oxidative stress. For example, **sulforaphane**, a bioactive isothiocyanate from broccoli, cabbage, and kale, is reported to induce the expression of phase II detoxification enzymes such as quinine reductase and glutathione S-transferase, and to enhance the transcription of tumor suppressor proteins. Its anticancer effects are exerted via inhibition of oxidative stress induced by the Nrf2-mediated pathways (Mileo and Miccadei 2016). Sulforaphane increases the expression of genes that directly detoxify exogenous toxins or endogenous ROS, and genes involved in the repair/removal of damaged proteins (Wang et al. 2012). Sulforaphane is proposed as an adjuvant of chemotherapy in several preclinical studies due to its ability to target cancer stem cells by regulating pathways such as NF-κB, Hedgehog, and Wnt/β-catenin (Li and Zhang 2013). Its antiproliferative effects have been demonstrated in pancreatic and human breast cancer stem cells (Mileo and Miccadei 2016). The **phenethyl isothiocyanate**, a dietary phytochemical also found in some cruciferous vegetables, is reported to inhibit histone deacetylase activity and restore the glutathione S transferase P1 expression through demethylation of specific gene promoter in many cancer types (Wang et al. 2007). However, recent studies have reported that phenethyl isothiocyanate that was used in studies of prostate cancer inhibited GSH peroxidase and complex III of the mitochondrial electron transport chain (Xiao et al. 2010). The **indole-3-carbinol** from broccoli, cauliflower, and collard greens, as well as its digestion derivate **diindolylmethane**, is found to induce the expression of Nrf2-mediated phase II drug-metabolizing and antioxidant (hemeoxygenase-1 and SOD1) genes. Their anticancer effects are demonstrated against hormone-responsive cancers like breast, prostate, and ovarian cancers (Wang et al. 2012).

Organic sulfides and polysulfides present in **garlic** and **onion** are considered potent antioxidants that enhance levels of glutathione in cells (Bilecova-Rabajdova et al. 2013). Diallyl-sulfide present in garlic is a powerful inhibitor of CYP2E1, which is related to some carcinogen metabolism (Bilecova-Rabajdova et al. 2013). In addition, the di-(1-propenyl) sulfide is reported to irreversibly inhibit oxidative enzyme lipoxygenase, which is overexpressed in several tumors, including breast, colorectal, and prostate cancer (Sobha and Andallu 2013). It is shown that the inhibition of lypoxygenases decreases cancer angiogenesis and growth (Sobha and Andallu 2013).

As will be discussed later, the majority of compounds mentioned above are reported to exert prooxidant effects, which makes their role in cancer treatment controversial. Thus, the efficacy and safety of antioxidant therapeutic interventions in cancer have to be demonstrated by accurately designed and conducted clinical trials, which is especially important if antioxidants are utilized in combination with the chemo/radiotherapy. Nevertheless, from a chemopreventive point of view, compounds with antioxidant effects are shown to play an important role, at least in delaying or preventing tumor development (Mileo and Miccadei 2016).

ROS-Elevating Strategy in Cancer Treatment

Due to enhanced ROS production, the cancer cells maintain a state of increased oxidative stress that promotes survival but also makes cells vulnerable to further increase in ROS levels over a cancer-specific threshold (Fig. 2). Numerous natural compounds have been reported to act as prooxidants that trigger ROS-mediated cytotoxicity and apoptosis in cancer cells. For example, **apigenin**, a natural polyphenol found in many plants including chamomile, has been reported to act against adenocarcinoma HT-29 and HCT-15 cell lines by reduction of the mitochondrial membrane potential (MMP) and production of free radical species. Its ability to suppress cell survival by inducing both apoptosis and G2/M-phase arrest is demonstrated in human colon cancer HCT116 cells, human melanoma cells, and ACC-2 cells. It is shown that apigenin modulates multiple signaling pathways, including PI3K/AKT, NF-kB, JAK/STATs, Wnt/β-catenin, AMPK, MAPK/ERK, and JNK, mainly by stimulating the accumulation of ROS that leads to induction of DNA damage (Vallejo et al. 2017). As noted earlier, the **caffeic acid** is reported to increase ROS production in cervical carcinoma HTB-34 cells and to activate 5′-adenosine monophosphate-activated protein kinase involved in cell energy regulation (Vallejo et al. 2017).

Bigelovin, a sesquiterpene lactone naturally produced by *Inula helianthus* aquatic, is found to increase ROS production and consequently induce a multicaspase activation, G2/M cell cycle arrest, and DNA damage in HT-29 and HCT116 colorectal cancer cell lines (Vallejo et al. 2017).

Linalool, monoterpenoid alcohol, is reported to induce apoptosis via hydroxyl radical-mediated oxidative stress in HCT116 and CCD-18Co cell lines (Vallejo et al. 2017).

It was found that diterpenes, **carnosic acid and carnosol** from rosemary, exhibit the capacity to regulate oxidative stress in different in vitro and cellular systems. A sharp increase of intracellular ROS that resulted in necrosis was observed in colon adenocarcinoma HT-29, SW480, and HGUE-C-1 cell lines. Rosemary extract strongly inhibited proliferation, migration, and colony formation of colon cancer cells (Perez-Sanchez et al. 2019).

Silibinin, a flavonolignan extracted from *Silybum marianum,* is shown to induce ROS production, which is correlated with the disruption of MMP, ATP depletion, and induction of autophagic cell death in human colon cancer cells and breast cancer cells. In addition, silibinin is reported to induce apoptosis and autophagy in MCF-7 breast cancer cells, which is concomitant with the downregulation of AKT, mTOR, and ERK (Abdal Dayem et al. 2016).

Epigallocatechin-3-gallate (EGCG), a polyphenol from green tea, has dual antioxidant and prooxidant roles. Acting as a prooxidant, the EGCG is shown to produce ROS by autooxidation, and to induce apoptosis in different cancer types, such as human lymphoblastoid B cells, myeloid leukemia, breast cancer, and hepatocarcinoma. The EGCG can activate the intrinsic apoptotic pathway through inhibition of the PI3K/AKT signaling pathway, followed by a decrease of the MMP and an increase of the intracellular level of Ca^{2+} (Abdal Dayem et al. 2016; NavaneethaKrishnan et al. 2019).

Piperine, a natural alkaloid from long pepper (*Piper longum* L.), has been found to initiate ROS-induced mitochondria-mediated apoptosis by inhibiting catalase activity in hepatocellular carcinoma while in human oral squamous cells, ROS elevation was associated with mitochondrial depolarization and activation of caspase-mediated apoptosis (NavaneethaKrishnan et al. 2019).

Capsaicin, the component of *Capsicum,* is shown to induce a rapid increase of ROS level followed by a disruption of MMP and activation of downstream caspase-3 in human colon cancer, pancreatic cancer, glioma, and prostate cancer (NavaneethaKrishnan et al. 2019).

Levistolide A, a natural compound from the traditional Chinese herb *Ligusticum chuanxiong Hort*, is reported to trigger the production of ROS and endoplasmic reticulum (ER) stress, and to cause apoptosis of both wild-type and p53−/− HCT116 cells (Yang et al. 2017).

Eugenol, a phenolic constituent of cinnamon (*Cinnamomum* spp.), is found to elevate the intracellular ROS levels, to activate the pro-apoptotic proteins, to up-regulate the cell cycle regulator proteins p53 and p21, and to suppress the expression and activation of NFκB, resulting in downregulation of NF-κB target genes. Its cytotoxicity is observed in HeLa cervical cancer cells, breast cancer, and colon cancer. Furthermore, a **cinnamaldehyde** and its derivate **2-hydroxycinnamaldehyde** are reported to act as prooxidants that increase the level of intracellular ROS, inhibit the cellular antioxidant enzymes, and also induce the activation of Nrf2 pathway in various cancer cells, including leukemia, melanoma, colon cancer, oral cancer, nasopharyngeal carcinoma, breast cancer, and hepatoma in vitro (Larasati and Meiyanto 2018).

Extracts of plants used in traditional medicine were also investigated for their prooxidant activity.

The extract of ***Calophyllum inophyllum*** is found to induce the elevation of intracellular ROS, the loss of MMP, and to trigger apoptosis in MCF-7 breast cancer cells (Shanmugapriya et al. 2017).

It is found that the extract of ***Annurca*** **apple** acts as prooxidant, increasing the level of thiobarbituric acid-reactive species, which leads to apoptosis in MCF-7 cells (D'Angelo et al. 2017).

The water-soluble extract of ***Citrus unshiu*** peel is demonstrated to induce ROS generation, the loss of MMP, and apoptosis in MDA-MB-231 human breast cancer cells (Kim et al. 2018).

Torilis japonica extract, commonly used for treating hemorrhoids, uterine tumors, and fever, is found to induce apoptosis through the generation of intracellular ROS, by regulation of the MMP via the AMPK/p38 MAPK signaling pathway in colorectal cancer cells (HCT116) (Kim et al. 2016).

The hexane ethanolic extracts of ***Brucea javanica*** (L.) Merr., used in local traditional medicine to treat various diseases, is reported to induce apoptosis in HT29 colon cancer cells through the caspase activation via the ROS production, and p53, Bax, and NF-κB involvement (Bagheri et al. 2018).

Conium maculatum extract is found to increase generation and accumulation of ROS and thus depolarization of MMP, DNA damage, and apoptosis in HeLa cells (Mondal et al. 2014).

Coleus forskohlii root ethanol extract is demonstrated to induce apoptosis in gastric carcinoma cells via mitochondrial pathways involving oxidant/antioxidant imbalance (Rajkumar and Malathi 2016).

Methanolic extract of ***Hiptage benghalensis*** is reported to dramatically enhance the generation of intracellular ROS and caspase-3 activity in a dose-dependent manner in HeLa, MCF-7, and human neuroblastoma IMR-32 cancer cell lines causing apoptosis (Bhukya and Yellu 2018).

Cratoxylum formosum leaf extract is found to induce ROS formation, increase caspase-3 activities, decrease the MMP, and cause apoptosis in HepG2 cells (Buranrat et al. 2017).

Water extract of ***Cistanche tubulosa,*** widely used in traditional medicine, is reported to increase intracellular ROS production and, consequently, cause the ROS-induced cell death in several human colon carcinoma cell lines (Al-Menhali et al. 2017).

Stryphnodendron adstringens (Mart.) Coville (Fabaceae) aqueous extracts are found to promote apoptosis in murine B16F10Nex-2 melanoma cells by the increase of intracellular ROS levels, and induction of MMP dysfunction (Baldivia et al. 2018).

Ethanolic extracts of ***Dendrobium crepidatum*** **and** ***Dendrobium chrysanthum*** are demonstrated to possess the cytotoxic and apoptosis-inducing activity against Dalton's lymphoma by increasing the intracellular levels of ROS (Prasad and Koch 2016).

Clinacanthus nutans hexane extract is reported to enhance the ROS production and to induce apoptosis via intrinsic and extrinsic caspase pathways in non-small cell lung cancer (A549), nasopharyngeal carcinoma (CNE1), and HepG2 cancer cells (Ng et al. 2017).

Annona muricata *Linn.*, a tropical plant used in ethnomedicine for the treatment of cancer, is reported to induce cytotoxicity in different cancer types through inhibition of ATP synthesis by blocking the mitochondrial complexes or by the promotion of apoptosis through upregulation of Bax and downregulation of Bcl2 (Abdul Wahab et al. 2018).

As already stated, numerous antioxidants demonstrate prooxidant activities as well, depending mainly on their dosage and oxidative state of the cell (Fig. 3). For example, **curcumin** is reported to induce cell death by ROS-induced mitochondrial DNA damage in human hepatoma cells, and autophagy in colon cancer cells through ROS-dependent activation of the ERK1/2 and the p38 MAPK pathway (Vallejo et al. 2017). Furthermore, in vitro and in vivo studies have indicated that aforementioned **quercetin** could selectively increase intracellular ROS levels and promote apoptosis, necrosis, and autophagy in a variety of cancers, including glioma, osteosarcoma, cervical and breast cancer, squamous cell carcinoma, lung, and hepatoma cancer cells (NavaneethaKrishnan et al. 2019). **Resveratrol** treatments of colon cancer (HT-29) are shown to increase ROS generation and to induce autophagy via the up-regulation of microtubule-associated protein 1 light chain 3-II (LC3-II) expression (Abdal Dayem et al. 2016). Moreover, resveratrol is reported to prevent tumor initiation and progression by stimulating apoptosis in prostate and neuroblastoma

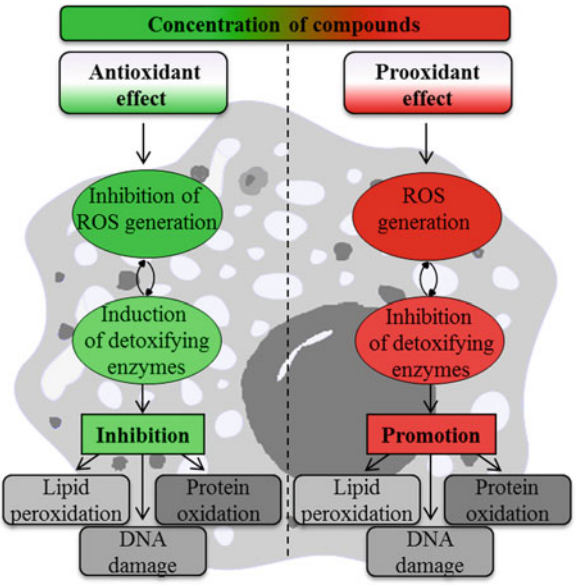

Fig. 3 Concentration-dependent effects of anticancer compounds

cells via activation of p53, ROS-dependent caspases, and death receptors for TRAIL and FasL (NavaneethaKrishnan et al. 2019). **Genistein** has shown a prooxidant action via mobilization of copper ions, which led to an increase in ROS generation, DNA damage, and apoptosis in breast cancer cells (Abdal Dayem et al. 2016). **Garlic extract** is found to be an inducer of oxidative stress in human leukemia (HL-60) cells. Its cytotoxicity involves a phosphatidylserine externalization, caspase-3 activation, and nucleosomal DNA fragmentation associated with the increased concentration of malondialdehyde (Vallejo et al. 2017). Also, the extract of **ginger** is shown to display an antiproliferative effect on several tumor cell lines by inducing a ROS-mediated autosis (Akimoto et al. 2015).

Numerous synthetic compounds are designed and investigated for their potential to be used as redox-directed anticancer therapeutics. It has been shown that metal drugs are redox-active substances that interact and disturb cellular redox homeostasis resulting in increased levels of oxidative stress (ROS generation) by different mechanisms. The current knowledge of various metal complexes regarding the input of redox processes in their anticancer activity is summarized in the following section.

The era of metal-based anticancer drugs began with the discovery of the anticancer properties of the **platinum** complex cisplatin (*cis*-$[PtCl_2(NH_3)_2]$). Several studies demonstrated that cisplatin-induced cytotoxicity is closely related to increased ROS generation that alters the MMP and damages the respiratory chain, which ultimately triggers the apoptotic process. Pt^{II}-based drugs, nedaplatin, lobaplatin, and heptaplatin act similar to cisplatin by targeting DNA. Two other Pt^{II} complexes, carboplatin and oxaliplatin, are the next most important metal-based anticancer

drugs used in chemotherapy against a wide variety of different solid tumors. Their anticancer activity is based on the formation of platinum-DNA adducts that lead to cell cycle arrest and apoptosis (Ndagi et al. 2017).

Iron complexes have been widely studied as potential anticancer drugs due to their ability to act as chelators and cause iron depletion and elevation of ROS levels that lead to oxidative DNA damage. Ferrocenium picrate and ferrocenium trichloroacetate salts are the first iron complexes reported possessing anticancer potency (Xie et al. 2017). It is shown that Fe(II) complexes pass through the cancer cell membrane by transferrin receptor (TfR)-mediated endocytosis and exhibit strong anticancer efficacy, suggesting that Fe(II) complexes with proper ligands could be promising chemotherapeutic agents for cancer treatment (Xie et al. 2017).

Numerous studies indicated that **ruthenium complexes**, Ru(II) and Ru(III) complexes, possess excellent antitumor characteristics with selective antimetastatic properties and low systemic toxicity. It is assumed that Ru compounds easily penetrate the tumor cells and bind effectively to DNA. The Ruthenium (II) polypyridyl complexes show an antiproliferative mechanism against osteosarcoma cells (MG-63). The complexes effectively inhibit cell migration, induce cell cycle arrest, and induce apoptosis of osteosarcoma cells through a ROS-mediated mitochondrial dysfunction pathway, which is accompanied with the regulation of the Bcl-2 family proteins expression (Xiao et al. 2018). Two novel ruthenium complexes containing piplartine are able to induce caspase-dependent and mitochondrial intrinsic apoptosis of HCT116 cells by ROS-mediated pathway (D'Sousa Costa et al. 2017). Also, the anticancer activities of two ruthenium (III) complexes with -fluoroquinolones norfloxacin and ofloxacin are based on their capacity to induce ROS formation and activation of the apoptosis in tumor cells (Gruia et al. 2015). Furthermore, the complex synthesized from the reaction of $[(\eta^6\text{-}C_6H_6)RuCl_2]_2$ with benzo[h]quinoline, 1,10-phenanthroline, and tbtfpip is reported to exhibit superior cytotoxicity compared to cisplatin in HeLa, A549, and multidrug-resistant (A549R) cancer cells. This compound acts via the induction of apoptosis by inhibition of thioredoxin reductase (TrxR), the elevation of intracellular ROS levels, mitochondrial dysfunction, and cell cycle arrest (Zeng et al. 2016). The complexes of the ruthenium(II) with *N*-alkylphenothiazine counter-ions (chlorpromazine hydrochloride, thioridazine hydrochloride, and trifluoperazine dihydrochloride, respectively) are found to disturb the viability and redox homeostasis in PC12 and U2OS cancer cell lines (Leskovac et al. 2018).

The generation of intracellular ROS by the reduction of Cu(II) to Cu(I) is considered the primary anticancer mechanism of **copper complexes**. Furthermore, Cu(I) can catalyze the formation of ROS and RNS to induce pro-apoptotic oxidative stress. The copper (II) 2-hydroxy-1-naphthaldehyde complexes are demonstrated to exhibit the chemotherapeutic effects by generating ROS and arresting the cell cycle in the G_0/G_1 phase in A-549 cells. These complexes effectively induce ER stress-mediated apoptosis, inhibit topoisomerase-1, and damage cancer DNA by a ROS-mediated mechanism (Khan et al. 2019). Three copper complexes with benzimidazole-derived scaffolds, and secondary ligands, 1–10-phenanthroline and 2,2′-bipyridyl, are reported to enhance ROS generation and induce apoptosis

followed by necrosis and, loss of plasma integrity in MCF-7 cancer cells (Hussain et al. 2019). Also, the nanocomposites (Cu-PANI) based on polyaniline (PANI) and copper nanoparticles are found to induce oxidative stress and consequent dysfunction of vital cellular processes, disruption of cell signaling pathways, and the induction of cell death through both apoptosis and necrosis (Bogdanović et al. 2018).

In the past few years, chemotherapeutic agents based on **palladium** were designed and synthesized against various types of tumors. Flubendazole, a benzimidazole carbamate, that was used to synthesize new Pd(II) complexes showed that the cytotoxicity of complexes against MCF7 cells varied with the change in the coordinated ion X (X = Cl-, Br-, SCN- and NO3-). [Pd(L)Cl] complex is shown to induce apoptosis of A549 cells via ROS-mediated mitochondria-dependent pathway (Wang et al. 2018a). The two mono-functional platinum complexes containing 8-substituted quinolone derivatives as ligands are reported to exhibit a significant in vitro cytotoxicity. The Mon-Pt-2 tends to accumulate in mitochondria and stimulate TrxR inhibition, ROS release, and an ER stress that is mediated by mitochondrial dysfunction and induction of apoptosis and autophagy (Wang et al. 2018a).

Many **gold complexes** show in vitro and in vivo anticancer activity through different mechanisms of action, including inhibition of the TrxR, increased generation of ROS, alteration of the cell cycle phases, and modulation of kinases (Altaf et al. 2019). Generally, Au complexes act on redox homeostasis of cancer cells by inhibition of the cytosolic and mitochondrial Trx system that leads to an increase of ROS, mitochondrial swelling, a decrease in MMP, and subsequently apoptosis. The bipyridine and bipyrimidine gold (III) dithiocarbamate-containing complexes show significant anticancer activity in a panel of human cancer cell lines. The most prominent is complex $[Au_2(BPM)(DMDTC)_2]Cl_4$ that induces ROS generation, double-stranded DNA breaks, and apoptosis, especially in prostate cancer cells (Altaf et al. 2019). Cyclometalated gold(III) complex $[Au(C^N)(dtc)]PF_6$ (HC^N = *N*,1,1,1-tetraphenyl-λ^5-phosphanimine) shows selective cytotoxicity toward T-cell leukemia Jurkat cells that could be attributed to mitochondria dysfunction induced by ROS and Bax/Bak activation (Altaf et al. 2019). Also, the [Au(NHC)Cl] (NHC = 1,3-diethylbenzimidazol-2-ylidene N-heterocyclic carbene) complexes are reported to act as potent TrxR inhibitors, increase ROS formation, inhibit mitochondrial respiration, induce apoptosis, and affect cellular metabolism (Altaf et al. 2019). These results are in accordance with our previously published studies reporting the prooxidant and cytotoxic effect of gold(III) complexes (Vujacic et al. 2011; Bondzic et al. 2017).

Although the mode of action of **silver complexes** (silver(I)) as anticancer agents have not yet been elucidated, studies on various cell lines have demonstrated that cell death induced by AgNPs is associated with the generation of ROS and involves mitochondria-dependent apoptosis. For example, the silver(I)–NHCs exhibit potent antiproliferative activity toward human cancer cell lines. Accumulation of intracellular ROS appears to be associated with the disruption of MMP and the release of cytochrome c into the cytosol, leading to apoptosis (AshaRani et al. 2009).

Combination Therapy

Traditional cancer treatments, including chemo- and radiotherapy, are mainly based on ROS-induced cytotoxicity in tumor cells. In addition, photodynamic anticancer therapy and some alternative approaches, such as immunotherapy and hormone therapy, all induce ROS production and ROS- dependent cytotoxicity. Therefore, it is reasonable to expect that further increase in cellular ROS by ROS-elevating agents could improve the therapeutic efficacy of traditional cancer treatments. Most of the chemotherapeutic drugs target mitochondria to induce ROS production and/or inhibit the cellular antioxidant enzyme system (Yang et al. 2018). For example, arsenic trioxide (ATO), which is approved for leukemia treatment, has been reported to disrupt the mitochondrial electron transport chain leading to an enhanced electronic leakage and an increased ROS production (Yen et al. 2012). Besides, the anthracyclines, platinum coordination complexes, and antitumor antibiotic bleomycin are also reported to affect mitochondria and induce enhanced ROS production (Marullo et al. 2013). The inhibition of antioxidant system during chemotherapy seen as depletion of cellular GSH and elevated ROS production is reported for drugs such as imexon, which has been investigated for the treatment of pancreatic, lung, breast, prostate, melanoma, and multiple myeloma cancers. Also, the Methoxyestradiol (2-ME), an anticancer agent currently under investigation, is reported to inhibit SOD and to induce ROS-mediated apoptosis in leukemia cells (Wang and Yi 2008).

Several studies indicate that some natural compounds with a prooxidant mode of action might synergize ROS-dependent chemotherapeutic drugs. It is shown that anthraquinone emodin synergized cytotoxicity of cisplatin, ATO, and doxorubicin in several types of cancer (Wang and Yi 2008). While low concentrations of quercetin attenuate the ROS-induced damage, the high concentrations appeared to enhance the cytotoxicity of cisplatin in ovarian cancer (Mut-Salud et al. 2016). Furthermore, a combination of curcumin and docetaxel are found to induce more potent cytotoxicity via an increase of ROS in metastatic prostate cancer (Vallejo et al. 2017). The trials combining EGCG with drugs such as doxorubicin, 5-FU, and cisplatin demonstrated its great potential as an adjuvant in chemotherapy (Mut-Salud et al. 2016). As reviewed by Mut-Salud et al., a competitive inhibitor of glycolysis, 2-deoxy-D-glucose, is found to increase the toxicity of paclitaxel while C6 ceramide is reported to promote a prooxidant effect of docetaxel (a derivate of paclitaxel) in breast tumor cells (Mut-Salud et al. 2016). Furthermore, the organotellurides are found to synergize with oxaliplatin probably via overproduction of H_2O_2 and ROS-induced mitochondria damage in colon cancer cells with no induced toxicity in normal tissues (Yang et al. 2018).

As for radiotherapy, numerous studies have shown that natural compounds could function as efficient radiomodulators (Joksic et al. 2008). The plant compounds with prooxidant mode of action, such as betulinic acid, curcumin, resveratrol, ellagic acid, and caffeine, are demonstrated to be efficient radiosensitizers, which operate synergistically with ionizing radiation and enhance the radiosensitivity of cancer cells (Ruba and Tamilselvi 2018). Besides plants, bioactive metabolites from some

microorganisms appeared to be efficient radiosensitizers as well. For example, studies on bacterial pigment undecylprodigiosin have demonstrated its radiosensitizing effects in irradiated human lymphocytes (Petrovic et al. 2017). Conversely, numerous natural antioxidants could function as chemoprotectors/radioprotectors, which reduce normal tissue toxicity and attenuate the side effects of therapy mainly via activation of antioxidant enzymes and inhibition of lipid peroxidation (Singh et al. 2018; Ruba and Tamilselvi 2018; Joksic et al. 2008, 2009; Jankovic et al. 2008; Petrovic et al. 2008).

The published data are currently inconclusive to address whether taking antioxidants, along with chemotherapy or radiotherapy, may have adverse effects on treatments. As comprehensively discussed by Singh et al. (2018), antioxidant supplementation during chemotherapy/radiotherapy could enhance therapeutic effectiveness and improve the patients' survival rate. On the other side, numerous reports have linked the intake of antioxidants with a loss of efficacy of the treatment, and even with increased mortality in patients who received antioxidants during both chemotherapy and radiotherapy (Mut-Salud et al. 2016).

Since interaction between anticancer drugs and antioxidants is more complicated than simple depletion or elevation of oxidative stress, it is expected that therapy outcome may depend on the type of antioxidant and its dosage, the cancer type and stage of the disease, the type, and level of endogenous ROS as well as the individual involved (Wang and Yi 2008).

Conclusion

Oxidative stress is one of the most important factors associated with the onset and progression of cancer. The differences in redox status, antioxidant enzymes expression, cell signaling, and transcription factor activation profiles of normal and cancer cells allow the use of these parameters for the design of new promising therapeutic strategies against cancer. Many synthetic and naturally occurring compounds are reported to be effective in oxidative stress-targeted cancer prevention and/or therapy. Both ROS-depleting and ROS-elevating strategies have been proposed for cancer treatment, each of them showing the advantages and disadvantages. There is no general recommendation of which approach to use because the final effect might depend on the individual involved, the type of cancer, the disease stage, and the type of the drug. In addition, the potential previous cycles of chemotherapy/radiotherapy may affect the outcome. Therefore, it is necessary to establish the guideline for each patient type and to determine the individual therapy regime, which will take into consideration basal antioxidant status, the diet of the patient and habits, type of cancer, stage of the disease, previous treatments, the type of the drug as well as the route of administration and dosage.

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