



The interplay between reactive oxygen species and antioxidants in cancer progression and therapy: a narrative review

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Objective: To unveil the role of reactive oxygen species (ROS) and antioxidants in signaling and involvement in cancer progression and therapy.

Background: Cancer is considered one of the main causes of mortality in developed countries and expected to be more in developing countries as well. Although some cancers may develop at young age, yet almost all types of cancers are an accumulation of genetic and epigenetic cell damages. Cancer is considered a diverse collection of diseases on a cellular level rather than a single disease; and each disease has a different cause as well. ROS have been seen as harmful toxic molecules; however, they are recognized for cellular signaling capabilities. Elevated levels of ROS have protumorigenic activities; they induce cancer cell proliferation, and adaptation to hypoxia in addition to other effects like DNA damage and genetic instability. They are produced excessively by cancer cells to hyperactivate cellular transformation meanwhile increasing antioxidant capacity to avoid cell death.

Methods: We discussed peer reviewed published research work from 1987 to 2021. In this paper, we review the role of antioxidants as defensive barrier against excessive ROS levels for maintaining oxidation-reduction (redox) balance; however, antioxidant can also strive in tumor cells with their scavenging capacities and maintain protumorigenic signaling and resist the cancer cell oxidative stress and apoptosis. High doses of antioxidant compounds could be toxic to cells as they are capable of reacting with the physiological concentrations of ROS present for normal cellular processes and signaling.

Conclusions: Maintaining cellular redox homeostasis is vital for healthy biological system. Therefore, therapeutic modalities for cancer including antioxidants and ROS management should be used at certain doses to target specific redox pathways involved in cancer progression without disrupting the overall redox balance in normal cells.

Keywords: Cancer; reactive oxygen species (ROS); antioxidants; signaling; oxidative stress

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Introduction

Reactive oxygen species (ROS) are molecules containing reactive oxygen that participate in cellular electron transfer (1). ROS were first studied for tumorigenesis

promoting activity in the mid-90s (2,3); however, their cellular homeostasis is essential for normal cell survival and proper cell signaling. Low ROS levels can activate signaling pathways in a regulatory manner that is essential for metabolic adaptation, differentiation and cellular

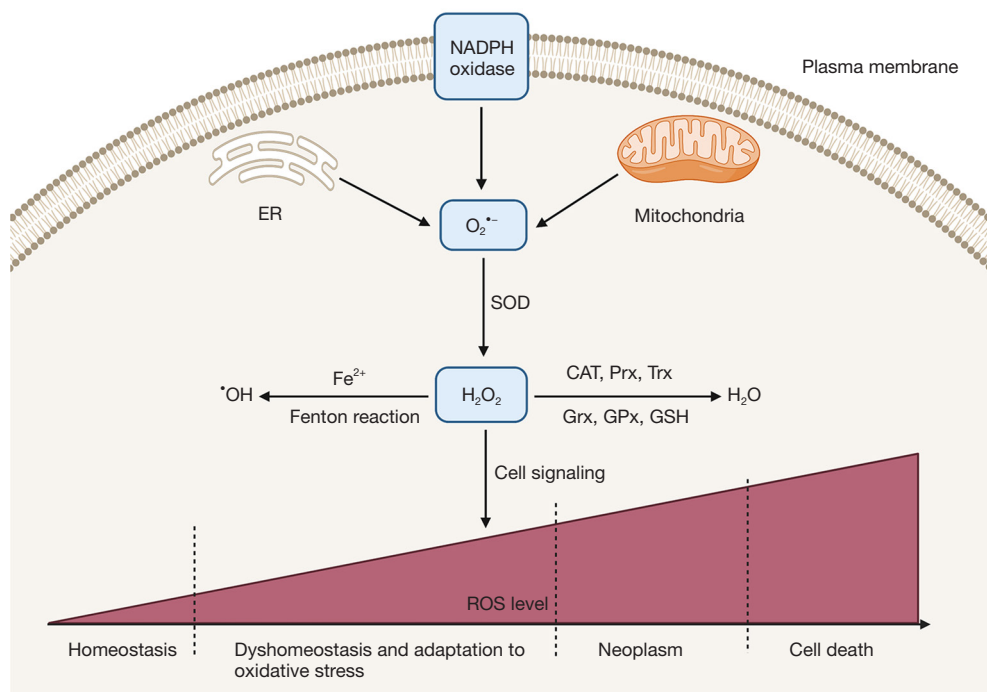


Figure 1 The vital roles of reactive oxygen species (ROS) and antioxidants in cancer progression and treatment. Redox homeostasis is a balance of ROS generation and elimination. Mitochondria, NADPH oxidase, and endoplasmic reticulum (ER) are the three main sources of ROS generation. Superoxide anion radical ($O_2^{\bullet-}$) is the principal form of ROS and can be rapidly converted into hydrogen peroxide (H_2O_2) by superoxide dismutase (SOD). H_2O_2 can be converted to hydroxyl radical ($\bullet OH$) in the presence of Fe^{2+} or Cu^{2+} ions via Fenton reaction or be catalyzed to H_2O by CAT (catalase), Prx (peroxiredoxins), Trx (thioredoxins; Grx (glutaredoxins), GPx (glutathione peroxidases), and GSH (glutathione). The concentration of ROS determines the cell fate: low levels of ROS are necessary for cell signaling and homeostasis; intermediate levels of ROS result in loss of cell homeostasis and increased adaptation to oxidative stress, and subsequent transformation to neoplasm; while a severe and prolonged increase of ROS leads to cell death. The figure was adapted from Barbara Marengo *et al.* 2016 (5) and created using BioRender (<https://biorender.com>, accessed on 17 July 2021).

proliferation (4) as presented in *Figure 1* (5).

ROS include hydrogen peroxide (H_2O_2), superoxide anion radical ($O_2^{\bullet-}$), and the hydroxyl radical ($\bullet OH$). These species have been suggested to be solely toxic and pathological molecules in the past years (6). However, it has been extensively studied for their control over various physiological reactions, including cell proliferation and differentiation, signaling, and adjustment to hypoxia (7,8). ROS have a critical role in both cell mitochondria-to-nucleus and membrane-to nucleus signaling pathways, regulating biochemical effectors, and also contribute to growth factor signal transduction (9,10).

Up-regulated ROS levels and down-regulated cellular antioxidant enzymes lead to different malignancies through different molecular factors like nuclear factor kappa B (NF- κ B) and nuclear factor (erythroid-derived 2)-like-2 factor

(NRF2) (11). ROS cause DNA damage via nucleobases oxidation such as guanine. Since oxidized pair is subjected to repair, it can lead to an error that causes mutagenesis. ROS have multiple sources among which are physical stressors like extensive exercise, aerobic and anaerobic exercise and radiation. Physical stress is found to produce oxidative stress and production of $O_2^{\bullet-}$ from mono-electric reduction of oxygen, which is considered as prototype for other ROS like H_2O_2 , $\bullet OH$ and ROO^{\bullet} (12), while radiation is among the most recognized sources for ROS and hence highly correlated with initiation of cancer (13).

The cellular main redox couples are: cysteine (Cys)/cystine (CySS), GSH/glutathione disulfide (GSSG), NADH/ NAD^+ , NADPH/ $NADP^+$, peroxiredoxin (Prx)-sulfiredoxin (Srx), and thioredoxin (Trx)/thioredoxin disulfide (TrxSS). These enzymes work with thiol redox to

control ROS levels (14). On the other hand, antioxidants were widely believed as protective agents against cancer as they have the ability to neutralize ROS and other free radicals causing DNA damage and leading to cancer, however many clinical trials failed to find an evident beneficial effect. Several epidemiological studies also show an inverse correlation between cancer and antioxidant-rich diets (15). For instance, total antioxidant capacity (TAC), measured through ferric-reducing ability of plasma score, was investigated in a study on total 393 pancreatic cancer patients and 353 pancreatic cancer-related deaths which concluded that lower TAC leads to higher incidence of pancreatic cancer (16).

In this review, we discuss the role of different ROS in cancer progression as well as their signaling role; and different antioxidants either exogenous or endogenous and their role in progression of different tumors. We present the following article in accordance with the Narrative Review reporting checklist (available at <https://dx.doi.org/10.21037/tcr-21-629>).

ROS acting as protumorigenic

Oxidative stress as one of the most leading causes of toxicity, is attributed to ROS interactions with cellular macromolecules like DNA, and proteins, which interfere with cellular pathways signaling molecules such as protein kinases, and transduction mechanisms (17). ROS are mainly categorized into $O_2^{\cdot-}$, H_2O_2 , $\cdot OH$, and lipid peroxides. ROS are continually produced or in contact with cellular components, since they are formed as byproducts of oxidative phosphorylation (OXPHOS), or mitochondrial electron transport in aerobic respiration and they are kept by enzymatic antioxidants into homeostatic state (18,19).

Elevated levels of ROS can occur by either ROS increased production or decreased elimination (20,21). Whilst ROS levels are excessive, H_2O_2 can easily diffuse away from their site of production, resulting in oxidative damage and cellular death. Therefore, ROS action as signaling molecules or pathological agents mainly relies upon the type of ROS, their concentration, and the concentration of antioxidants (22).

H_2O_2 is the most reported signaling molecule (23,24). H_2O_2 is a product of two electron reduction of O_2 . It is produced by at least thirty H_2O_2 generating enzymes like superoxide dismutase (SOD), xanthine oxidase and NADPH oxidase (NOX) (25). Due to its physiochemical properties, H_2O_2 molecules are capable of carrying redox signal from its

site of generation to their target sites. The mechanism by which H_2O_2 contributes in cellular signaling is the oxidation of cysteine residues to maintain protein function (26).

ROS signaling molecules are either formed in mitochondria or via membrane bound NOXs, while we have 10 sites for $O_2^{\cdot-}$ production in mitochondria, the $O_2^{\cdot-}$ molecules contributing to redox signaling are the ones derived from mitochondrial complexes I, II, and III, while H_2O_2 is derived from the action of SOD 1, 2 and 3 (SOD) on $O_2^{\cdot-}$ (27,28). As $O_2^{\cdot-}$ is released in the mitochondria, it is readily converted by SOD2 into H_2O_2 (29). SOD1 acts to detoxify $O_2^{\cdot-}$ within the mitochondrial intermembrane space producing freely diffusible H_2O_2 .

NOXs have a role in both ROS generation and detoxification, as membrane bound NOX is one of the major oxidants in cancer. Both NADPH 1–5 and Dual Oxidases 1, 2 (DUOX 1,2) contribute to H_2O_2 and $O_2^{\cdot-}$ production by either one electron or two electron reduction of oxygen (30). Although NOX is localized mainly in plasma membrane, it can also be found in nucleus membrane, mitochondrial membrane, and membrane of endoplasmic reticulum. Additionally, $O_2^{\cdot-}$ has shown to have a role in redox signaling and the initiation of cell death (31). $\cdot OH$ is formed when H_2O_2 undergoes Fenton chemistry with ferrous or cuprous ions, leading to damage of lipids, proteins, and DNA. In case of ROS abundance, metastasis of many types of cancers including breast, prostate, and ovarian cancer is correlated with their cellular redox state (32), as redox imbalance will lead to a mitogen activated protein kinases (MAPK) signaling cascade which is involved in tumor cell migration (33). The phosphatidylinositol 3-kinase and protein kinase B (PI3K/Akt) survival pathway which are activated in most cancers, are found to be induced by ROS (34). Moreover, the oncogenic activation of Akt increases ROS production which promotes cancer cell proliferation (35).

In another study, Ras oncogenic mutations were found to increase NOX4 mediated ROS generation which enhances tumor proliferation (36). NOX4 also contributes to certain types of malignancies, such as renal cancer. NOX4 was found in an ATP bound inactive form in inner mitochondrial membrane. When activated after ATP redistribution and metabolic reprogramming, it gives rise to anticancer drug resistance. Similarly, in ovarian and breast cancer, with overexpression of NOX4, and H_2O_2 -dependent nonsense mutations, resulting in the tumor promoting behavior of NOX4 as well as anticancer therapy resistance (37). Another study has shown that inhibition of NOX generated ROS will lead to a decreased potential

for tumorigenesis in diverse cancer types, e.g., inhibited NOX generated ROS in pancreatic cancer treated with flavoprotein inhibitor diphenylene iodonium (DPI), resulted in apoptosis through AKT/ apoptosis signal regulating kinase 1 (ASK1) pathway (38).

When a proliferative tumor outgrows their main blood supply, regions of the solid tumor enter a state of hypoxia and low glucose supply implying more ROS generation. Cancer cell will then activate metabolic pathways which will stabilize *hypoxia-inducible factors* (HIFs), activating AMP-activated protein kinase (AMPK) to enhance NADPH production in an attempt to maintain redox balance (39). Tumor cells adapt to hypoxia by activating glucose metabolism; as tumor cells use glycolysis whether there's oxygen deficiency or not, this results into a more aggressive phenotypes, in a phenomenon known as Warburg effect (40). Glycolysis plays an essential role in redox homeostasis through transportation of metabolic intermediates such as pentose phosphate pathway (PPP) which activates overproduction of reducing agents like glutaminolysis-generated GSH and NADPH, thus tumor cells adapt to glucose deprivation by increasing glycolysis to compensate the excessive production of ROS and inhibit glucose-hydroperoxide cell death (41). Moreover, during hypoxia, the HIF- α protein and HIF- β protein subunits are dimerized, translocated to the nucleus and incite the expression of proangiogenic genes like vascular endothelial growth factors and other genes for cancer cell survival and metastasis (42,43). HIF- α protein stabilization through ROS dependent mechanism is found to promote tumorigenesis of certain cancer cells (43,44).

It is also evident that the ratio between $O_2^{\cdot-}$ and H_2O_2 determines whether it will induce cell survival or cell death. The ratio predominates in favor of increased $O_2^{\cdot-}$ as in tumor cells where antioxidants are ineffective; this condition will promote cell survival by means like activating PI3K/Akt H⁺ efflux pumps which will eventually result in cancer proliferation or progression. Whereas the ratio is in favor of H_2O_2 , this induces cell death signaling by cytosolic acidification (activated caspases), mitochondrial death factors recruitment, and exerting inhibitory effect on intracellular $O_2^{\cdot-}$ production and accumulation.

Since ROS change cellular processes as a result of changing protein function, the disulfide redox state will then be changed leading to cancer, by the action of NOX or xanthine oxidase (45). ROS can also initiate pro-oncogenic signaling pathways, e.g., KRAS transformation which is found in numerous cancerous cells and contribute to cancer

cells intrusion and relocation. For instance, mutations in Kelch-like ECH-associated protein 1 (KEAP1), NRF2 or the KRAS oncogenes result in enhanced ROS scavenging through NRF2-mediated gene expression in cancer cells to maintain ROS homeostasis and prevent ROS mediated activation of death-inducing JNK/p38, causing irreversible oxidative damage to cancer cell. Mutations in Keap1 and NRF2 have been associated with many cancers including colon, breast, gastric and liver cancer, thus NRF2 is an important factor for cancer cell tumorigenesis and proliferation (43,46).

It is yet unclear how proteins are specifically targeted and efficiently oxidized by H_2O_2 , given the extensive and multicompartmental cellular antioxidant system, however a suggested mechanism for targeted protein oxidation by H_2O_2 is due to ROS scavenging enzymes that can transduce the H_2O_2 signals (47). The impact of ROS in relation to protein oxidation, as mild oxidative function in protein signaling, is a reversible process (disulfide, sulfenic acid and sulfinic acid formation), while the terminal oxidation into sulfonic acid leads to a complete loss of protein function (48). Higher ROS levels may cause post-translational modification of histidine, methionine, and cysteine. The widely known mechanism for H_2O_2 to achieve their cellular regulatory function is by redox-balance of cysteine residue by redox-sensitive proteins. Cysteine is oxidized by H_2O_2 into cysteine sulfenic acid (Cys-SOH) or disulfide (cystine). With exposure to ROS, thiol group of cysteine residues in proteins like transcriptase, phosphatase and kinase is oxidized (49-52).

The p53 tumor suppressor gene is found to play a regulatory role in ROS accumulation by inducing the expression of several antioxidant genes like SOD2, glutathione peroxidase 1 (GPX1), and catalase (CAT), thus when p53 is exposed to mutation or loss of function, ROS accumulation is observed in more than 50% of human cancers (53,54). Mutations of p53 were found to enhance angiogenic response in ROS mediated activation of vascular endothelial growth factor A (VEGF-A) and HIF-1 in HCT116 human colorectal carcinoma cells (55). A recent study on liver cancer cells, treated with rhein, the main active compound of rhubarb medicinal plant, has concluded cell cycle arrest and apoptotic pathway via excessive ROS generation which in time activates c-Jun N-terminal kinases (JNK/Jun/caspase-3) signaling pathway in HepG2 and Huh7 cells (56).

TP53-induced glycolysis and apoptosis regulator (TIGAR) has been found to promote tumor chemotherapy

resistance, as it has been overly expressed in cancer and oncotherapy as in tamoxifen resistance in MCF-7, and dasatinib resistance in chronic lymphocytic leukemia, additionally it decreases ROS in tumor cell eventually promoting its growth (57). The 5-fluorouracil (5-FU) as an antimetabolite drug, generates mitochondrial ROS by p53 dependent pathway (58). It was also found that p53-mediated ferroptosis, a nonapoptotic form of cell death, leads to p53-dependent inhibition of the cysteine-glutamate antiporter xCT (SLC7A11), which subsequently elevates ROS levels (59).

Antioxidants acting as protumorigenic

Cancer patients have been taking antioxidants as an alternative medicine in form of nutritional supplement, either after or during conventional cancer therapy, often at higher doses than recommended dietary allowance (RDA), in an attempt to improve the quality of life for cancer patients (60,61); yet there is no sufficient evidence that antioxidants have such beneficial effects. On the other hand, some studies suggested that using antioxidant with the conventional concentrations may not be sufficient to counter the high yield of reactive oxygen metabolite produced, and may then promote cell proliferation and malignancy progression (62). Other *in vitro* and *in vivo* data concluded that antioxidants selectively inhibiting tumor cell progression, may alter cellular redox balanced status, leading to an enhanced cytotoxic effect of the therapy (63-66).

The suggested rationale for using antioxidant supplementation during chemotherapy, is to compensate the total antioxidant decline (measured by total radical antioxidant parameter/serum micronutrients) due to depletion of antioxidants after treatment, as some studies tried to investigate the effect of a single or a combination of antioxidants with chemotherapy; yet the evidence for such depletion isn't conclusive (67). The antioxidant system in our bodies have two main groups, endogenous antioxidants (enzymatic or non enzymatic) e.g., glutathione (GSH), glutathione peroxidase (GPx), CAT and SOD among many others, while exogenous antioxidants such as vitamins (E and C), polyphenols or carotenoids which can be taken from diet as a main source or supplement in other conditions (68,69). Both endogenous and exogenous antioxidant system work synergistically to maintain the cellular redox homeostasis.

Despite the fact that *in vitro* studies have highlighted the cytoprotective effect of dietary antioxidant constituents like polyphenols or carotenoids against oxidative stress or

cell death, they can also display prooxidant activity, such as a number of polyphenols known by their antioxidant activity like catechin, epicatechin and quercetin, in a high concentration or in the presence of metal ions (70-72). The strong reducing power of antioxidants may affect the metal ions e.g., Cu^{2+} , Fe^{3+} , increasing their ability to form hydroxyl radicals in high concentrations through Fenton reaction from peroxides (73,74).

In this regard, several studies concluded that polyphenols in higher concentrations then serve as prooxidants (75,76), e.g., quercetin at higher concentrations ($>50 \mu\text{M}$) can initiate ROS generation especially $\text{O}_2^{\cdot-}$; and in another study, it was observed to decrease cell viability, and TAC (77). Flavonoids such as fisetin were also investigated and found to cause cytotoxicity and apoptosis at higher concentration (50–250 μM), while at lower concentration (10–25 μM), they have protected rat H4IIE cells from H_2O_2 induced cytotoxicity (71). Flavonoids also have the ability to generate ROS at higher concentrations via autoxidation e.g., myricetin (78,79). Antioxidant phenolics, have free radical scavenging activity, they give rise to a relatively stable phenoxyl radical, due to delocalization of the unpaired electrons on the aromatic ring (80). However, these stable phenoxyl radicals can induce cellular damage through DNA oxidation, resulting in mutagenesis (75). The chelating power of phenolics may also influence their prooxidant activities, *in vitro*. The pH of the medium is also found to affect redox abilities of phenolic compounds, so at physiological pH (pH 7.4), chelating activity may be affected, certain phenolics have displayed prooxidant activity, while at lower pH values, the antioxidant activity may prevail (72,81).

N-acetyl-L-cysteine (NAC) was used as exogenous antioxidant to investigate the role of ROS in tumor processes in animal models, and was found to cause impaired p53-null lymphoma and lung cancer growth through prevention of DNA oxidation and subsequent mutagenic events (82). However other studies suggested that NAC promotes tumor imitation and metastasis in mouse models of melanoma and lung cancer (83-85). Another research study reported that NAC increases melanoma metastasis *in vivo* through small guanosine-triphosphatase activation (86). Moreover, in a study on pancreatic ductal adenocarcinomas (PDAC) treated with NAC, the microRNA 135a and microRNA 135b (miR-135a and miR-135b) (a class of small endogenous non-protein coding RNAs capable of altering the expression of target genes and has a role in inhibiting invasion of cancer cell),

were shown to decline (87). Like NAC, vitamin E has a role in lung cancer and melanoma initiation and progression (83,84). A very large trial with selenium and vitamin E comprising 35,533 men from 427 different study sites found no reduction in prostate cancer risk in healthy individuals taking either selenium or vitamin E (88). In a randomized double-blind, placebo-controlled trial of AMATERASU, analysis was performed for 417 postoperative patients at stage I to stage III digestive tract cancer from the esophagus to the rectum, to whom a dose of 2,000 IU/day vitamin D3 was administered. Programmed death-ligand 1 (PD-L1) as an anticancer immunity counter expression of cancer cells, was found to be upregulated. PD-L1 was measured through ELISA, divided into five quintiles; and vit D supplementation was found to significantly reduce the risk of relapses and death to approximately 30% of the highest quantile of serum PD-L1 (89).

In another a study with Finnish male smokers being given alpha-tocopherol and beta-carotene (ATBC trial), a higher lung cancer rate was observed in the treatment group (90,91). A larger trial composed of men and women with risk of lung cancer were given beta-carotene and retinol, and the trial was stopped due to high incidence of mortality in antioxidant treatment group. Another study observed no significant results when beta-carotene was administered to healthy women (92). Carotenoids were also found to increase mortality in breast cancer patients (93). Moreover, the correlation between increased risk of lung cancer and beta-carotene and vitamin A intake has drawn wide attention to the possible role of antioxidants in cancer progression (94). Furthermore, fucoxanthin (carotenoid organic pigment) also acts as prooxidant at higher concentrations increasing cellular ROS and extracellular signal regulated kinase (ERK) 1/2 and p38 MAPK protein phosphorylation in murine hepatic BNL CL.2 cells, while in lower concentration, it functioned as antioxidant (95). Lycopene as a carotenoid was used in ovarian cancer study and resulted in downregulation of signal transduction of transcription factor STAT 3 which propagates tumorigenesis and mutation with deregulated cell apoptosis (95).

Vitamin C supplements in combined treatment with doxorubicin have shown to increase its activity in breast cancer (96). However, a high dose of vitamin C has been observed to function as ROS generator inducing the cell death of KRAS- and BRAF-mutant colon cancer cells (97). Another study showed that Vitamin C can be autoxidized to dehydroascorbate (DHA) increasing cellular oxidative stress (98). However, it is suggested

that at its physiological doses, vitamin C antioxidant activities outweigh its prooxidant ones (99). Another study reported that high doses of vitamin C were cytotoxic to MCF7 and MDA-MB231 cells representing luminal and basal-like breast cancer due to oxidative stress induced by high ascorbate doses and ROS accumulation with high disruption of glycolysis and ATP levels dropping. These high ascorbate concentrations inhibited TCA cycles and increased oxygen consumption (100).

Resveratrol demonstrated the ability to trigger apoptosis in tumor cells at relatively high concentrations (101). However, resveratrol was found to increase hydroxyl radical's formation in presence of copper ion, having prooxidant activity (102,103). Another study found that resveratrol effectively enhanced Nk cells, which is a trending approach in cancer treatment, and also increased interferon gamma (IFN- γ) levels along with interleukin-2 (IL-2). Additionally, NK cellular activity was boosted in both human and mouse whole blood upon resveratrol introduction (104). A number of flavonoids was further investigated for their effect on colon cancer cell lines. Naringenin, catechin and epicatechin were introduced with concentration range 5 and 25 μ M; which resulted in decreasing mitochondrial metabolic activity, inhibiting protein kinase C (PKC) signaling pathway, and increasing ROS generation which subsequently induces ROS mediated apoptosis. This intracellular ROS mediated apoptosis is revealed to be concomitant with increased caspase activity (105).

Campesterol, a plant secondary metabolite steroid with antioxidant properties, was investigated in human ovarian cancer cell lines. It resulted in impaired ROS production and mitochondrial function. In a dose dependent manner, both ER stress sensor proteins expression and ROS generation were increased, as well as inhibition of cell cycle progression through PCNA and PI3K/MAPK signal pathways. Campesterol synergistically increased the activity of chemotherapeutic agents as cisplatin and paclitaxel (106). This correlation between antioxidants and ROS mediated cellular apoptosis is illustrated in *Figure 2*.

In diabetic patients, it has been found that multiple cancers development like breast, liver and colon cancer, are of high incidence (107). Many clinical trials have suggested that supplementation should be avoided for people with high risk of developing cancer (108). The antidiabetic drugs used to modulate glucose metabolism, which will have long term effects on diabetic patients, also affect the insulin-like growth factor-1 axis or other factors associated with cancer initiation and progression (109). A common class

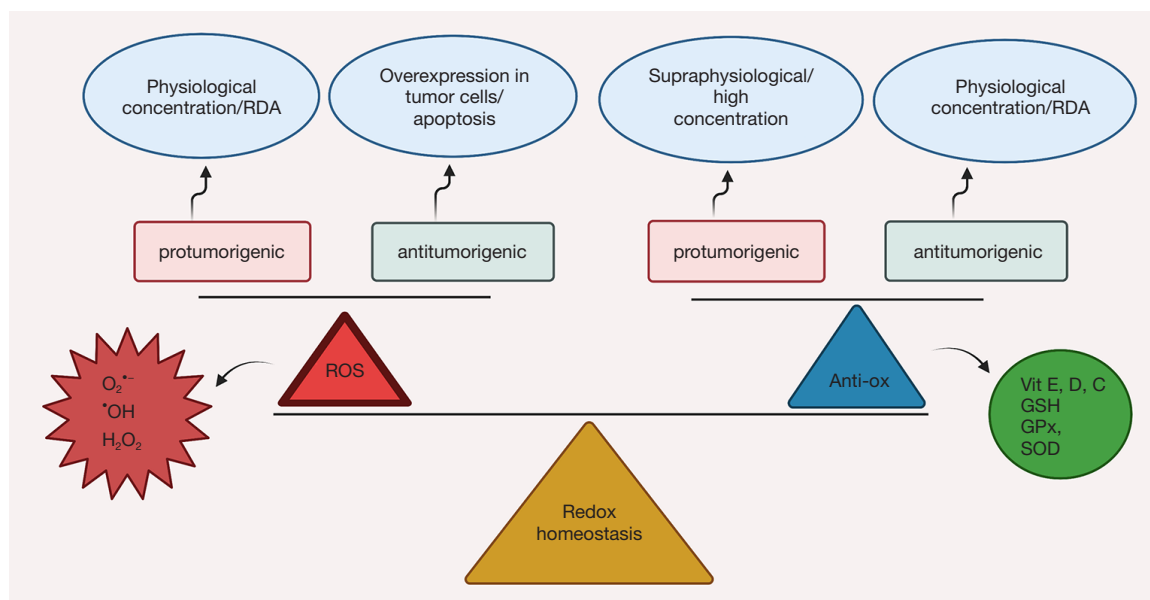


Figure 2 The link between antioxidants (exogenous or endogenous) and reactive oxygen species (ROS) as a counter force for each other into keeping redox homeostasis; both species act either antitumorigenic or protumorigenic depending on their physiological concentration/dosing system. Recommended dietary allowance (RDA) and anti-ox denote the recommended dietary allowance and antioxidant respectively.

of antidiabetics, dipeptidyl peptidase-4 inhibitors (DPP-4i), saxagliptin and sitagliptin were investigated, along with the antioxidant, antineuropathic α -lipoic acid (ALA) for possible association with cancer incidence. No clinical evidence was found to support that DPP-4i drugs either alone or combined with other drugs, increases the risk for cancers (110). However, ALA is proven to induce prolonged activation of the nuclear factor E2-related factor 2 (NRF2) (111), which eventually enhances cancer cells invasive capacity and mobility, and accelerates tumor metastasis; although it does not increase the incidence of cancer. As a consequence of the mentioned intricate effects, antioxidants should be administered with caution to cancer patients.

Conclusions

There has been a change in the perception of ROS and antioxidants over time; as ROS have been considered as toxic molecules and been highlighted once again for their cellular signaling role, however the role of ROS in cancer progression should be extensively investigated as it may lead to development of therapeutic modalities for treatment of malignancies. Additionally, while antioxidants were thought to be exclusively beneficial, however in high doses they

have been shown to contribute to tumor progression. ROS management strategies for cancer cases were trialed by using antioxidant therapy, yet with the failure of antioxidant trials as cancer therapy, a need has emerged for alternative therapies. The balance between prooxidant and antioxidant is vital for the healthy biological system, and the majority of chemotherapy disrupts the redox balance not only in cancer cells, but also in normal ones which activates adaptive responses, so when developing approaches for cancer treatment based on ROS accumulation, the antioxidant pathways that are selectively used by cancer cell must be taken into consideration.

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Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at <https://dx.doi.org/10.21037/tcr-21-629>)

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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