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Mini-review

Dietary phytochemicals with anti-oxidant and pro-oxidant activities: A double-edged sword in relation to adjuvant chemotherapy and radiotherapy?

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ABSTRACT

Many advances have been made in the development and introduction of new anti-cancer drugs to the clinic. However, limited attention has been paid to improving the efficacy of currently available treatments through complementary phytochemical interventions that affect cellular reactive oxygen species (ROS) levels, which are important for the etiology of certain cancers and the effectiveness of radiotherapy and some chemotherapy. In this regard, the maintenance of redox homeostasis may be influenced by the intake of anti-oxidant and pro-oxidant compounds from dietary sources. Interestingly, certain dietary phytochemicals exhibit both anti-oxidant and pro-oxidant activities, depending on their concentration and cellular microenvironment. There is evidence that concurrent administration of some dietary phytochemicals enhances the efficacy of certain cancer treatments by increasing intracellular ROS accumulation. Paradoxically, consumption of the same dietary phytochemicals under conditions that result in the scavenging of ROS might also negatively affect the outcome of ROS-dependent cancer treatments. This review discusses the potential impact of consuming dietary phytochemicals with anti-oxidant and/or pro-oxidant activities on the effectiveness of concurrent chemotherapy and/or radiotherapy in cancer patients.

1. Introduction

1.1. Dietary phytochemicals and their anti-cancer activity

A large number of dietary phytochemicals, also known as phytonutrients or plant secondary metabolites, possess disease-fighting capabilities if regularly ingested in efficacious amounts [1]. These phytochemicals are abundant in fruits, vegetables and plant-derived products such as tea, wine, and spices. Many studies have suggested that the regular intake of fruits and vegetables, as well as supplements containing purified dietary phytochemicals, may be effective in the prevention and/or control of various types of cancer [2–14]. These anti-cancer activities have been, at least in part, attributed to the anti-oxidant (substances that delay or prevent the oxidation of other substances) and/or pro-oxidant (substances that increase oxidative stress) properties of different dietary phytochemicals. Furthermore, some phytochemicals may be used in combination with chemotherapy or radiotherapy with the aim of improving the potency of these treatments or reducing drug-associated adverse side effects. Here we review the anti-oxidant and pro-oxidant properties of various dietary phytochemicals and discuss their potential to impact the effectiveness of chemotherapy- and/or radiotherapy-based treatments of cancer at a molecular level, as well as the clinical implications of their use.

1.2. Reactive oxygen species and oxidative stress

Reactive oxygen species (ROS) are formed within cells as a by-product of oxygen metabolism; however, ROS levels can undergo a substantial increase in response to external stimuli such as environmental stress, ionizing radiation, chemical agents and hypoxia [15–17]. ROS are chemically reactive due to the presence of an unpaired electron in the outermost electron shell and, as a result, can cause oxidative damage to key cellular components such as nucleic acids, lipids, and proteins. The most physiologically significant ROS are superoxide anion radicals ($O_2^{\bullet -}$), hydrogen peroxide (H_2O_2) and hydroxyl radicals ($OH^{\bullet}$) – see supplemental Table 1 for a complete list of endogenous ROS. The

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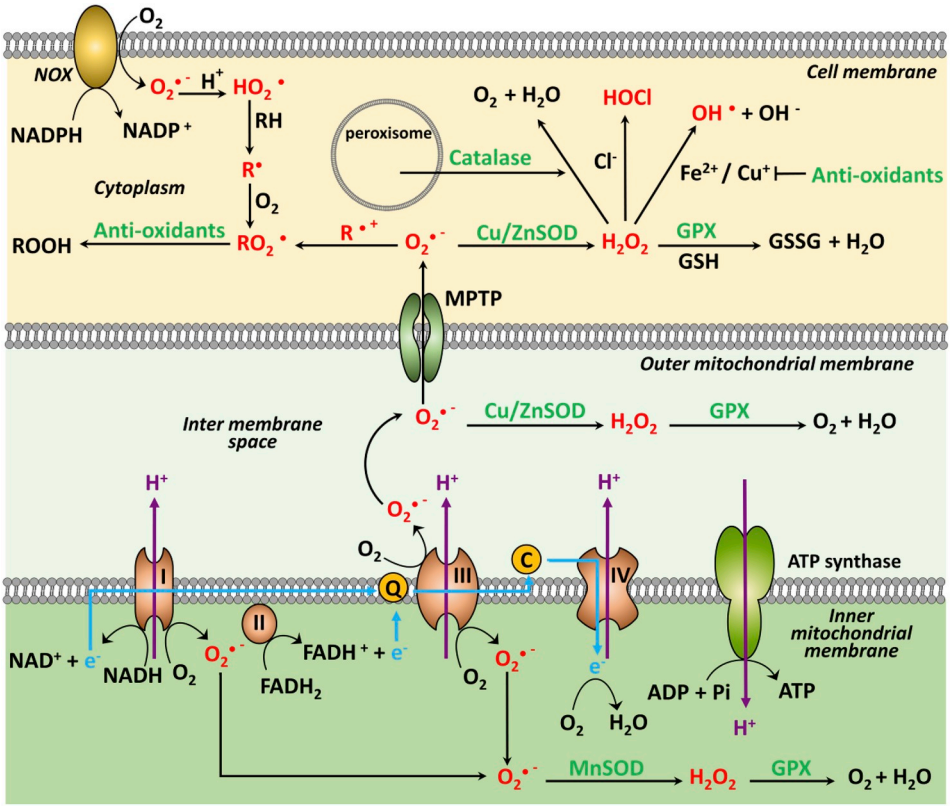

Fig. 1. ROS-generating and ROS-scavenging systems maintain cellular redox homeostasis.

The majority of $O_2^{\bullet -}$ is produced by the complex I and III as a by-product of the electron transport chain at the inner mitochondrial membrane. The synthesized $O_2^{\bullet -}$ can be converted to H_2O_2 by SODs. $O_2^{\bullet -}$ released to the mitochondrial matrix and intermembrane space is reduced to H_2O_2 by MnSOD and Cu/ZnSOD, respectively. Some $O_2^{\bullet -}$ is also released into the cytoplasm *via* the mitochondrial permeability transition pore, which can then be reduced by Cu/ZnSOD to produce H_2O_2. $O_2^{\bullet -}$ generation using extracelluar O_2 is mediated by NOX. In the presence of transition metal ions such as Fe^{2+} and Cu^{2+}, $O_2^{\bullet -}$ generates $OH^{\bullet}$, the most reactive ROS through the Fenton reaction.

O_2: molecular oxygen; **$O_2^{\bullet -}$**: superoxide anion; **$HOO^{\bullet}$**: hydroxyperoxyl radical; **RH**: alkyl groups; **$R^{\bullet}$**: alkyl radical; **$R^{\bullet +}$**: alkyl cation; **H^+**: hydrogen ion; **ROOH**: lipid hydroperoxide; **HOCl**: hypochlorous acid; **H_2O_2**: hydrogen peroxide; **$OH^{\bullet}$**: hydroxyl radical; **H_2O**: water molecule; **Cl^-**: chloride ion; **OH^-**: hydroxyl ion; **Fe^{2+}**: ferrous ion; **Cu^+**: cuprous ion; **NOX**: NADPH oxidase; **MnSOD**: superoxide dismutase 1; **Cu/ZnSOD**: superoxide dismutase 2; **GPX**: glutathione peroxidase; **GSH**: glutathione; **GSSG**: glutathione disulfide; **MPTP**: mitochondrial permeability transition pore; **NADPH**: nicotinamide adenine dinucleotide phosphate; **$FADH_2$**: Flavin adenine dinucleotide; **e^-**:electron; **ATP**: adenosine triphosphate; **ADP**: adenosine diphosphate; **Pi**: inorganic phosphorus; **Complex I**: NADH-ubiquinone oxidoreductase; **Complex II**: succinate dehydrogenase; **Complex III**: cytochrome bc1; **Complex IV**: cytochrome c oxidase; **Q**: ubiquinone; **C**: cytochrome c.

Red texts: Most significant intracellular radicals contributing to oxidative stress.

Green texts: Components of the cellular antioxidant defense system.

Blue arrows: Flow of electrons through mitochondrial electron transport chain.

Purple arrows: Pumping of hydrogen ions (protons) in mitochondrial electron transport chain.

majority of $O_2^{\bullet -}$ is produced by complex I (NADH-ubiquinone oxidoreductase) and complex III (cytochrome bc1) as a by-product of the electron transport chain located at the inner mitochondrial membrane. The $O_2^{\bullet -}$ that is released into the mitochondrial matrix, and intermembrane space is reduced to H_2O_2 by superoxide dismutases (SODs) 1 (MnSOD) and 2 (Cu/ZnSOD), respectively. Smaller amounts of $O_2^{\bullet -}$ are generated by nicotinamide adenine dinucleotide phosphate (NADPH) oxidases (NOX) and xanthine oxidases (Fig. 1). An additional source of intracellular ROS comes into play when certain phytochemicals induce the generation of extracellular H_2O_2 that diffuses into the cell and is converted to highly reactive $OH^{\bullet}$ *via* the Fenton reaction [18].

Homeostasis of intracellular ROS is maintained by a dynamic equilibrium. Basal levels of intracellular ROS play a vital role as signaling molecules in pathways involved in cell proliferation, growth, survival, and differentiation [19], as well as ion transport [20], by inducing oxidative modification of signal transduction pathway components [21–27]. These low levels of ROS also induce kinase activation and phosphatase inhibition, which results in phosphatidylinositide 3-kinase/protein kinase B (PI3K/Akt)-mediated cell survival and proliferation. However, the accumulation of excessive intracellular ROS results in oxidative stress and associated damage to nucleic acid bases, side chains of amino acids, and double bonds of polyunsaturated and monounsaturated fatty acids [28]. Thus, high levels of intracellular ROS cause oxidative modifications to PI3K and Akt, as well as other redox-sensitive components of the PI3K/Akt pathway, resulting in cell death [29]. Akt regulates intracellular ROS *via* inhibition of the transcription factor Forkhead box O (FoxO) [30], which induces the activation of SODs, catalase, and sestrin that subsequently inhibit mechanistic target of rapamycin (mTOR) through 5′ adenosine monophosphate-activated protein kinase (AMPK) activation [31]. As a result, Akt is also able to reduce the threshold of oxidative stress required for cancer cell death by suppressing anti-oxidant defense mechanisms and increasing mitochondrial ROS production [32]. However, mTOR induces a negative feedback loop that downregulates Akt *via* inhibition of PI3K activation. Collectively, activation of mTOR and inhibition of Akt increase cancer cell death, possibly through ROS-induced necroptosis [32–34]. Dysfunction of the mitogen-activated protein kinase (MAPK) pathway can lead to permanent cell cycle arrest or uncontrolled cell proliferation; however, cross-talk between ROS and the MAPK pathway components determines the outcome. The three most prominent subtypes of MAPK are extracellular regulated kinase (ERK) 1/2, c-Jun amino-terminal kinase (JNK) and p38 MAPK. Interestingly, MAPK activation occurs at different ROS levels that are specific to each kinase subtype [29,35]. At low or moderate levels of ROS, ERK1/2 is activated, leading to cell proliferation and survival [29]. Conversely, at high ROS levels, the MAPK pathway inhibits cell growth through the activation of JNK and p38 MAPK [35,36], which leads to the expression and activation of pro-apoptotic proteins (c-Jun and p53) and suppression of anti-apoptotic proteins (Bcl-2, Bcl-xL, and Mcl-1) [29]. Several dietary phytochemicals are able to inhibit the MAPK pathway *via* ROS scavenging and plant polyphenols, particularly flavonoids such as catechins, flavones, flavonols, flavonones, and anthocyanins, play a leading role in altering such ROS-mediated cell signaling. For example, epigallocatechin gallate (EGCG) is a catechin component of green tea that inhibits UVB-induced ROS production and subsequent activation of ERK1/2, JNK, and p38 MAPK in normal human epidermal keratinocytes [37]. Activation of ERK1/2, JNK, and p38 MAPK is inhibited when HeLa human cervical cancer cells are pretreated with resveratrol, a polyphenolic compound

found in grapes [38]. Apigenin, a flavone found in celery, induces the apoptosis of ARO human anaplastic thyroid carcinoma cells by down-regulating the c-Myc transcription factor, which is the nuclear substrate of ERK1/2. However, apigenin treatment does not affect MAPK protein levels [39]. Curcumin, a diarylheptanoid found in turmeric, does not affect the expression of ERK1/2 and p38 MAPK by HCT116 human colon cancer cells [40]. However, the JNK-specific inhibitor SP600125 reverses apigenin-induced apoptosis, suggesting the involvement of JNK-dependent pathways in apigenin-mediated apoptosis of HCT116 cells [40].

Mitochondria and peroxisomes are the two main sites of intracellular ROS production [41–43]; however, the Fenton reaction can generate ROS both inside and outside of cells. Inevitable ROS production during the process of oxidative phosphorylation in the mitochondria is considered the main source of intracellular ROS. Endogenous antioxidant defense mechanisms and the regular intake of dietary antioxidants can assist in balancing cellular ROS levels, leading to "ROS homeostasis" [44]. Intracellular ROS elevation is associated with initiation of aberrant cellular functions such as altered metabolic activity (switch from the metabolism of molecular oxygen by oxidative phosphorylation to inefficient aerobic glycolysis and increased activity of NOX), impaired mitochondrial and peroxisomal function, increased activity of enzymes involved in genetic and epigenetic alterations in carcinogenesis, receptor-mediated signaling and oncogene activation [22,45–48], leading to increased cell proliferation, and resistance to apoptosis, metastasis and angiogenesis [49,50]. Therefore, these aberrant cellular events are often used to characterize the malignant phenotype of the cell. An imbalance between ROS-generating (pro-oxidant) and ROS-scavenging (anti-oxidant) systems favoring excessive ROS generation disturbs the redox homeostasis, resulting in oxidative stress. Almost all cancer types undergo aerobic glycolysis (Warburg effect) [51,52], and their malignant phenotypic characteristics are maintained by constitutive activation of multiple cell survival signaling pathways together with the complete or partial shutdown of apoptotic pathways [53–58]. A high rate of metabolism and genetic alterations promote elevated ROS levels in cancer cells compared to non-malignant cells [49]. Furthermore, a moderate increase in ROS levels favors increased cell proliferation and survival of cancer cells and can be sustained through the activation of alternative anti-oxidant systems within the cell [59].

1.3. Hormesis

Hormesis is a biological phenomenon that explains the biphasic dose-response behavior of an oxidative stress-inducing natural substance, pharmaceutical drug or toxin [60]. According to this phenomenon, a biologically active molecule such as a phytochemical, when given at a low concentration, elicits a positive response (low dose stimulation) for adaptation or protection from the stress factor; however, the positive response is diminished, resulting in a toxic response, when the stress factor is present at a higher concentration (high dose inhibition) [60–62] (Fig. 2). Thus, hormetic phytochemicals exhibit anti-oxidant activity at low doses, which is weakened and superseded by pro-oxidant activity at high doses [63–66] (Fig. 2). For example, resveratrol at low concentrations (20 μM) exerts anti-oxidant activity, significantly reducing caspases 3 and 8, γ-glutamyltransferase (γ-GT), glutathione-S-transferase (GST) activities and malondialdehyde content in human blood mononuclear cells [67]. However, at high concentrations (50 μM), resveratrol shows pro-oxidant activity, causing lipid peroxidation, cellular damage and diminished proliferation that results in the death of human hepatic stellate cells [68]. Similarly, at low concentrations (< 10 μM), curcumin prevents the depletion of glutathione (GSH), and lipid peroxidation of erythrocytes whereas GSH levels are gradually decreased when the concentration of curcumin is increased, thus showing the hormetic activity of curcumin [69].

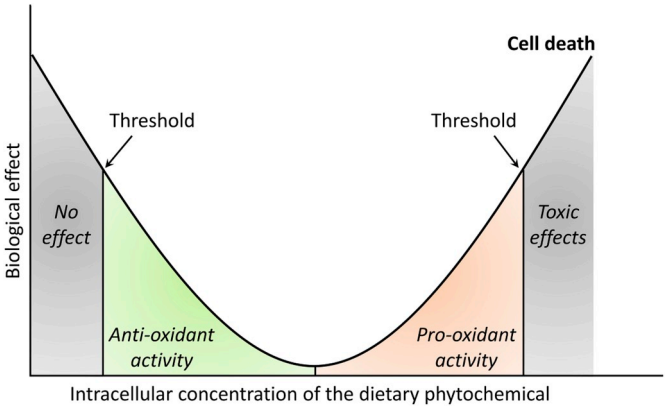

Fig. 2. Hormetic drug response curve of a typical dietary phytochemical with both anti-oxidant and pro-oxidant activity. Hormesis is a biological concept that explains the biphasic dose-response behavior of a natural substance, stress agent, pharmaceutical drug or toxin. Hormetic phytochemicals demonstrate low-dose stimulation and a high-dose inhibition. Certain dietary phytochemicals exhibit anti-oxidant activity at low doses that is overwhelmed by pro-oxidant activity at high doses.

2. Molecular basis of pro-oxidant and anti-oxidant properties of dietary phytochemicals

"Pro-oxidant" refers to substances that increase oxidative stress by inducing the production of ROS, reactive nitrogen species, and reactive sulfur species. Polyphenols are a major class of phytochemicals known to possess both anti-oxidant and pro-oxidant activity, depending on their concentration and the nature of the cellular microenvironment [70,71]. Generally, high concentrations, low pH and/or the presence of redox-active transition metal ions, causes certain phytochemicals to exhibit pro-oxidant activity [70]. Thus, elevated intracellular metal ion levels due to the over-expression of metal ion transporters (e.g., iron-transporting transferrin receptor 1 and copper transporter 1) may have a direct effect on the pro-oxidant activity of polyphenols. It is believed that the altered metabolic pathways of cancer cells promote increased cellular metal ion concentrations through a cancer cell-specific phenomenon known as the Warburg effect, which involves excessive aerobic glycolysis [72]. Most cellular macromolecules, including DNA, are pH-sensitive. Hence, low pH can destabilize chromatin proteins and the double helix structure of DNA, exposing chromatin-bound copper. The increased copper ion concentration in the cytoplasm can induce ROS-mediated oxidative stress by catalyzing polyphenol oxidation [73]. Similarly, at low pH levels, destabilization of hemoglobin releases iron in hemoglobin which can complex with the transferrin receptor 1 [74,75], leading to increased iron uptake by cells that enhances the ability of certain polyphenolic compounds to exert their pro-oxidant activity through iron-dependent ROS production in the cytoplasm *via* the Fenton reaction [71,76]. Polyphenols can also indirectly induce the production of ROS by affecting NOX expression [77] (Fig. 1).

Halliwell and Gutteridge defined anti-oxidants as "*any substance that, when present at low concentrations compared to those of an oxidizable substrate, significantly delays or prevents oxidation of that substrate*" [78]. Dietary anti-oxidants (mainly polyphenols) are widely found in fruits, vegetables, medicinal plants, grains, and edible macro fungi. Dietary anti-oxidants mitigate excessive ROS-induced oxidative stress by scavenging or converting ROS into less reactive and thus less dangerous species. Anti-oxidants neutralize ROS by accepting or donating an electron to eliminate the "unpaired electron status" of ROS. Endogenous ROS-scavenging complexes could be either enzymatic or non-enzymatic [79]. Most anti-oxidant phytochemicals contain a stable aromatic ring system that facilitates the delocalization of the unpaired electron of ROS. For example, the anti-oxidant network of lipid soluble α-tocopherol (vitamin E) and water-soluble ascorbic acid (vitamin C),

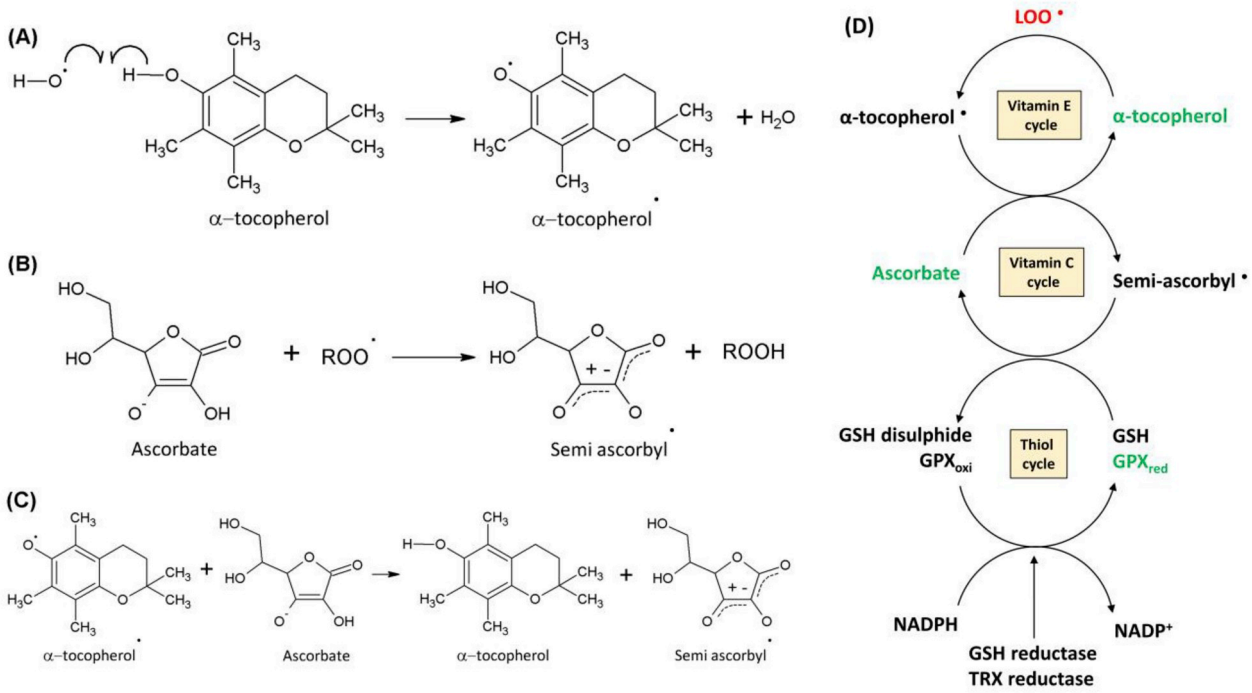

Fig. 3. Anti-oxidant network of vitamin E, vitamin C and thiol cycles in the scavenging of ROS. The anti-oxidant network of lipid soluble α-tocopherol (vitamin E) and water-soluble ascorbic acid (vitamin C) together with thiol cycle shows the coordination between multiple anti-oxidant systems in scavenging excessive ROS. **ROO•**: peroxyl radical; **OH•**: peroxyl radical; **LOO•**: lipid peroxide; **GPX_{oxi}**: oxidized-glutathione peroxidase; **GPX_{red}**: reduced-glutathione peroxidase; **GSH**: glutathione; **NADPH**: nicotinamide adenine dinucleotide phosphate; **TRX**: thioredoxin.

together with the thiol cycle, shows the coordination between multiple anti-oxidant systems in ROS-scavenging function [80] (Fig. 3). In comparison to $OH^{\bullet}$, $O_2^{\bullet -}$ is comparatively less reactive toward cellular ROS targets. Nevertheless, in the presence of Fe^{2+} and Cu^{+}, $O_2^{\bullet -}$ generates ROS such as H_2O_2 and $OH^{\bullet}$ through the Fenton reaction [19,50] (see Fig. 1 and reactions ① and ② under supplementary information). The enzymatic components of the endogenous anti-oxidant defense system include SOD1, SOD2, SOD3, catalase, glutathione peroxidase (GPX), glutathione reductase (GRd), glutathione-S-transferase (GST), thioredoxine reductase (TrxR), heme oxygenase (HO), cyclooxygenase (COX) and biliverdin reductase (see Fig. 1 and reactions ③ to ⑬ under supplementary information).

Kelch-like ECH-associated protein 1/nuclear factor erythroid 2 p45 (NF-E2)-related factor/anti-oxidant response element (Keap-1/Nrf-2/ARE) signaling is one of the most significant mechanisms of controlling redox homeostasis; many phytochemicals mediate their anti-oxidant activities through the regulation of this pathway (Fig. 4). The Nrf-2 transcription factor protects cells from oxidants, xenobiotics, electrophiles, and genotoxic agents *via* activation of a series of downstream effector molecules. Nrf-2 is negatively regulated by its suppressor protein, Keap-1, which prevents Nrf-2 stabilization and nuclear translocation under normal physiological conditions. Elevated ROS oxidizes the cysteine residues of Keap-1, resulting in its dissociation from Nrf-2 [81]. Activation of the Nrf-2 pathway leads to the expression of ARE-driven phase II antioxidant enzymes, phase II drug metabolizing enzymes, and drug transporters [81,82]. However, due to the cross-talk between Nrf-2 and multiple other cell survival and/or cell death pathways components, Nrf-2 activation can lead to either tumor-promoting or tumor-suppressing activities.

Most cancer types show elevated inherent Nrf-2 activity as a result of the activation of oncogenes such as K-Ras, B-Raf, and c-Myc, leading to increased cancer cell proliferation and survival [83]. Blockade of Nrf-2 signaling may, therefore, be an attractive target for chemotherapy. On the other hand, a mild to moderate elevation in genotoxic agents or oxidative stress stimulates the activation of p21 and p53 tumor suppressor genes, leading to cell cycle arrest or senescence as an adaptation mechanism [84]. Activated p21 binds to Nrf-2, preventing Keap-1-dependent Nrf-2 ubiquitination and triggering Nrf-2-dependent anti-tumor effects *via* cell cycle arrest related to the p53/p21 axis. In this regard, curcumin induces the expression of anti-oxidant enzymes, HO and GSH, by upregulating Nrf-2 expression in primary cultures of human cerebellar granule neurons, as well as suppressing ROS production by decreasing the GSH/glutathione disulfide (GSSG) ratio [85]. Curcumin-induced HO upregulation that is mediated through the inactivation of the Keap-1-Nrf-2 complex, followed by increased Nrf-2 binding to ARE is seen in human renal epithelial cells [86]. In addition, curcumin restores GST and NQO1 levels through Nrf-2 activation in T-cell lymphoma-bearing mice, suggesting that curcumin exerts Nrf-2 inducing activity *in vivo* [87]. EGCG exerts a chemo-preventive effect by inducing the Nrf-2 pathway, which leads to the expression of phase II metabolizing enzymes and anti-oxidant enzymes [88]. Quercetin, a plant flavonol compound that is present in most vegetables and fruits, induces Nrf-2 activation and subsequent GST activation in BJ foreskin fibroblasts and HaCaT skin keratinocytes [89]. Quercetin also induces the transcription of NQO1 through activation of the Nrf-2 pathway in HepG2 human hepatocellular carcinoma cells. Specifically, quercetin increases Nrf-2 mRNA and protein expression by inhibiting the ubiquitination of Nrf-2 and reducing post-translational levels of Keap-1 without affecting Keap-1-Nrf-2 dissociation [23]. Resveratrol reverses cigarette smoke-induced oxidative stress, and GSH depletion in alveolar epithelial cells by increasing Nrf-2 nuclear translocation and triggers increased γ-glutamyl cysteine ligase expression [90]. Taken together, these observations indicate that dietary intake of certain anti-oxidants directly influences Nrf-2 activation, leading to stimulation of cellular stress-response mechanisms.

3. Chemotherapy- and radiotherapy-induced ROS production

A number of chemotherapeutic drugs induce intracellular ROS accumulation that promotes either apoptotic or non-apoptotic (necrosis,

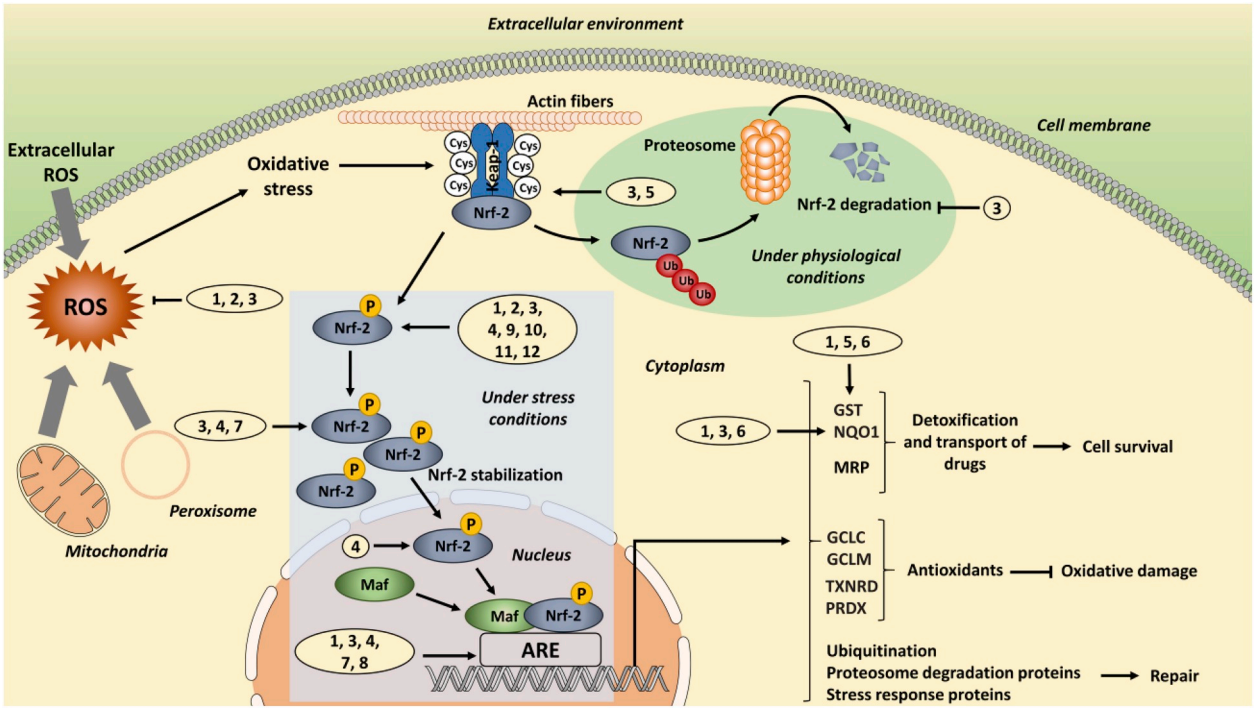

Fig. 4. Dietary phytochemicals exert anti-oxidant activity by triggering Keap-1/Nrf-2/ARE signaling and subsequent upregulation of downstream genes. Keap-1/Nrf-2/ARE signaling is a significant means of controlling redox homeostasis. Many phytochemicals mediate their anti-oxidant activities through the regulation of this pathway. Nrf-2 is negatively regulated by its suppressor protein, Keap-1, which interferes with Nrf-2 stabilization and nuclear translocation under normal physiological conditions, leading to its ubiquitination and subsequent degradation. Under conditions of oxidative stress, the Nrf-2 pathway is activated. ROS oxidizes the cysteine residues of Keap-1, resulting in its dissociation from Nrf-2. Stabilized Nrf-2 can then translocate to the nucleus and bind to the anti-oxidant response element (ARE) along with other transcription factors. Activation of the ARE leads to the expression of ARE-driven genes that encode proteins responsible for the neutralization of ROS, metabolism of xenobiotics and drug transporters. Because of cross-talk between Nrf-2 and multiple other cell survival and/or cell death pathways components, Nrf-2 activation can result in either tumor-promoting or tumor-suppressing activities. Nevertheless, blockade of Nrf-2 signaling may be an attractive target for chemotherapy.

1: Curcumin; **2**: Epigallocatechin gallate; **3**: Quercetin; **4**: Resveratrol; **5**: Isothiocyanate; **6**: Diallyl sulfide; **7**: Kaempferol; **8**: Mangiferin; **9**: Garlic organosulfates; **10**: Cafestol; **11**: Kahweol; **12**: Myricetin.

ROS: reactive oxygen species; **Cys**: cysteine; **Keap-1**: Kelch-like ECH-associated protein 1; **Nrf-2**: nuclear factor erythroid 2 p45 (NF-E2)-related factor; **Ub**: ubiquitin; **Maf**: musculoaponeurotic fibrosarcoma protein; **ARE**: anti-oxidant response element; **GST**: glutathione-S-transferase; **NQO1**: NADPH quinone oxidase-1; **MRP**: multidrug resistance-associated protein; **GCLC**: glutamate-cysteine ligase catalytic subunit; **GCLM**: glutamate-cysteine ligase modifier subunit; **TXNRD**: Thioredoxin reductases; **PRDX**: peroxiredoxin.

necroptosis, autophagy or mitotic catastrophe) death of cancer cells [91,92]. Anti-oxidant-based chemoprevention is mainly achieved by enhancing the expression of ROS-scavenging enzymes such as PEG-conjugated SOD, GPX, and CAT [93–96], by inhibiting the expression of NOX (e.g., minodronate and histamine) [77,97–99], and by manipulating nitroxide compounds (e.g., tempol) [100]. Pro-oxidant-based cancer treatments involve the administration of certain anti-cancer drugs, either alone or as a component of combination therapy to directly induce the generation of ROS in tumor cells (e.g., emodin and photodynamic therapy) [101,102] or inhibit the endogenous anti-oxidant defense system of the cancer cell (e.g., buthionine sulfoximine, metaxifin gadolinium, and disulfiram) [103–105]. Procarbazine and rituximab are two pro-oxidant anti-cancer drugs used in the treatment of Hodgkin's lymphoma and non-Hodgkin's lymphoma, respectively [106]. Doxorubicin, an anthracycline used in the treatment of many cancers, including breast cancer, bone cancer, and leukemia, also causes ROS accumulation in cancer cells [107]. However, excessive induction of ROS by certain chemotherapeutic agents also contributes to undesirable drug toxicity.

Radiotherapy is an effective means of local and loco-regional tumor control [108–110] that is practiced both in neoadjuvant (before surgery) [111,112] and adjuvant (after a surgery) [113,114] settings. Subjecting cancer cells to ionizing radiation results in immediate cell death (direct cell death) or cell death over a period of time (indirect cell death) [109,115]. In direct cell death, DNA damage is irreparable and lethal whereas indirect cell death is associated with radiation-induced ROS production as a result of radiolysis of cellular aqueous components [116–118]. Because normal cells proliferate at a slower rate than cancer cells, any damage caused to normal cells by radiotherapy is soon corrected by DNA repair mechanisms; however, rapidly dividing cancer cells lack the ability to promptly correct DNA damage and, indeed, often suffer permanent DNA damage. Collectively, these events lead to the radiation-induced selective death of cancer cells. Unfortunately, cancer cells can adapt to stressful conditions such as treatment-induced oxidative stress and become resistant to chemotherapy and/or radiotherapy. For example, Okon and co-workers have reported that a specific gefitinib-resistance clone of H1650 human lung cancer cells is associated with elevated intracellular ROS levels [119]. Moreover, ROS-mediated transformations in the tumor microenvironment lead to radioresistance of gastric cancer cells [120], while high ROS levels correlate with the radioresistance of prostate cancer cells [121]. Therefore, in order to achieve the maximum therapeutic outcome of chemotherapy and/or radiation therapy, ROS need to be maintained at an optimal level within the cancer cells and in the tumor microenvironment. The pros and cons of dietary phytochemicals with regard to chemotherapy- and radiotherapy-induced ROS are discussed below.

4. Impact of pro-oxidant and anti-oxidant properties of dietary phytochemicals on concurrent chemotherapy and/or radiotherapy

Both anti-oxidant and pro-oxidant activities are sometimes attributed to the same dietary phytochemical; therefore, despite their health benefits, these dietary phytochemicals need to be consumed with caution in patients who are receiving ROS-dependent chemotherapy and/or radiotherapy. The development of novel chemotherapeutic agents for the treatment of cancer is an area of extensive research, but little attention has been paid to improving the potency of existing therapies. The impact of GSH, vitamin E and N-acetylcysteine administration on cancer has been evaluated using single arm studies [122–126], randomized controlled trials [127–129], double-blind placebo-controlled randomized trials [130,131] and non-randomized trials [132]. Despite the positive outcome of these clinical trials, the impact of concurrently administered dietary anti-oxidants and/or pro-oxidants on the effectiveness of chemotherapy and/or radiotherapy is still a subject of debate. Some clinical data suggest that the concurrent administration of anti-oxidant supplements can help alleviate adverse drug side effects and improve the potency of chemotherapy and/or radiation treatment while other studies have shown that anti-oxidants protect tumor cells from oxidative damage caused by chemotherapy and/or radiation treatment [115,133,134]. For example, Cozzaglio and co-workers report that concurrent administration of oral GSH reduces cisplatin- and 5-fluorouracil-induced nephrotoxicity in colorectal cancer patients [123]. In addition, a randomized, double-blind, placebo-controlled trial conducted using a cohort of 540 head and neck cancer patients showed that administration of high dose α-tocopherol and β-carotene during radiotherapy improved patient quality of life by reducing adverse side effects associated with radiotherapy [135]. Malignant cells often show upregulated expression of glucose transporter (GLUT) [136,137], which leads to the intracellular accumulation of ascorbic acid, the reduced form of dehydroascorbic acid [138,139]. As a result, ascorbic acid tends to offer greater protection effect against oxidative stress in malignant cells than in non-malignant cells [140]. A double-blind, randomized trial conducted using 54 oral cavity and oropharynx cancer patients receiving radiotherapy showed a significant decrease in the incidence of symptomatic oral radio-induced mucositis with concurrent vitamin E intake; however, no any significant impact on the patient survival was detected [141]. Similarly, the concurrent administration of β-carotene, vitamin C, niacin, selenium, coenzyme Q10, and zinc with systemic chemotherapy do not impact disease-free survival of non-metastatic breast cancer patients [142], suggesting that anti-oxidants fail to worsen or improve conventional cancer treatment [142]. Indeed, studies on negative impacts resulting from the concurrent administration of dietary anti-oxidants with chemotherapy have concluded no statistical significance of positive correlation [141,142].

The design of most chemotherapeutic drugs and radiotherapy treatment regimens takes into account the remarkable differences in the effect of oxidative stress on non-malignant and malignant cells [143]. Indeed, it has been suggested that concurrent intake of anti-oxidants might lead to the de-sensitization of cancer cells to treatment [144]. In this regard, ROS have a biphasic effect on the expression of multidrug-resistant proteins [145–147]. Increased oxidative stress upregulates the expression of P-glycoprotein (P-gp), whereas anti-oxidants reverse P-gp overexpression [145,148–150]. It is therefore likely that the anti-oxidant activity of dietary phytochemicals may increase chemosensitivity of cancer cells by inhibiting P-gp expression.

Demonstration of pro- or anti-oxidant activity of phytochemicals *in vivo* has been a challenging area of research. The presence of cysteine and glutathione conjugates of EGCG in mouse urine following intraperitoneal administration of high doses of EGCG has been interpreted as an indication of EGCG oxidation, although these conjugates are not detected in urine after intragastric administration of EGCG [151]. The few clinical trials that have been published to date have been conducted using polyphenol-rich food or beverages in which the synergistic activity of phytochemicals is predictable. Furthermore, ingestion of pure polyphenolic compounds might not adequately reproduce the concept of “dietary polyphenol intake”. Oral administration of dietary polyphenols (more specifically, flavonoids) results in extensive phase II conjugation reactions that reduce available hydroxyl groups as well as “free flavonoids” [152]. Therefore, interpretation and correlation of human clinical trial data with *in vitro/in vivo* data are challenging. Multiple clinical trials have demonstrated that polyphenols do not downregulate biomarkers of oxidative damage such as F2-isoprostanes in plasma and F2-isoprostanes, isoprostane metabolites, 8-hydroxy-2′-deoxyguanosine (8OHdG) in urine, indicating that polyphenols-induced systemic anti-oxidant or pro-oxidant activity may in fact not exist [106,153–155]. On the other hand, dietary polyphenols may impact other biological activities in the human body that could interfere with their pro-oxidant and/or anti-oxidant activities. In addition, the stability of oxidative damage biomarkers in biological systems has not been well studied. Wu and co-workers found that oxidative stress biomarkers are stable over 36 h in blood; however, the total stability profiles of biomarkers were inconclusive [156]. Therefore, stability profiles and minimum detectable levels of these biomarkers in plasma and urine need to be established using experimental animal models and clinical trials. Moreover, published literature on the anti-oxidant and pro-oxidant activity of phytochemicals in humans does not report sufficient details of the biological samples that were studied. Taken together, these findings emphasize the need to gain a deeper understanding of the role and activity of dietary anti-oxidants and pro-oxidants in humans.

5. Conclusion and future directions

The potential for differential effects of ROS on cancer development and progression together with the hormetic behavior of many dietary phytochemicals further complicates our understanding of the impact of dietary phytochemicals on redox homeostasis. In addition, some clinical trial data challenges the well-established *in vitro* anti-oxidant activity of well-studied dietary phytochemicals, indicating the need for further research into the mechanisms responsible for the dual activity of such phytochemicals. Nevertheless, the molecular mechanisms involved in the anti-oxidant and/or pro-oxidant activities of many dietary phytochemicals have been detailed in a number of *in vitro* studies, but with the caveat that these mechanisms have not been adequately validated *in vivo*. Therefore, the *in vitro* and *in vivo* expression and stability of oxidative stress biomarkers needs to be further studied to confirm the anti-oxidant and/or pro-oxidant activity of dietary phytochemicals.

It is important to note that very few dietary phytochemicals have been approved for clinical use or for concurrent administration with chemotherapeutic drugs and/or radiotherapy. This review provides insights into the potential impact of dietary anti-oxidants and pro-oxidants at the molecular level on chemotherapy and radiation treatment (Fig. 5); however, it is still too early to conclude that ingestion of dietary phytochemicals is beneficial during cancer treatment. In fact, certain phytochemicals may be beneficial while others may be harmful. Clearly, there is a need for additional studies to better understand the precise role of dietary phytochemicals in cancer treatment. Furthermore, most of the currently available data have been generated from studies that have been designed around a single type of cancer. Even though these studies demonstrate the behavior of particular cancer in patients consuming anti- or pro-oxidant dietary supplements during the treatment, they do not provide adequate information on their impact on the treatment of other types of cancer. Studies focusing on multiple types of cancer need to be conducted in the future to overcome this limitation. Intra- and/or inter-tumoral heterogeneity is a major factor that determines whether particular cancer will respond to conventional treatment without or with concurrent administration of dietary supplements [157–159]. This is another limitation that many studies have not considered in their experimental design. Another important aspect

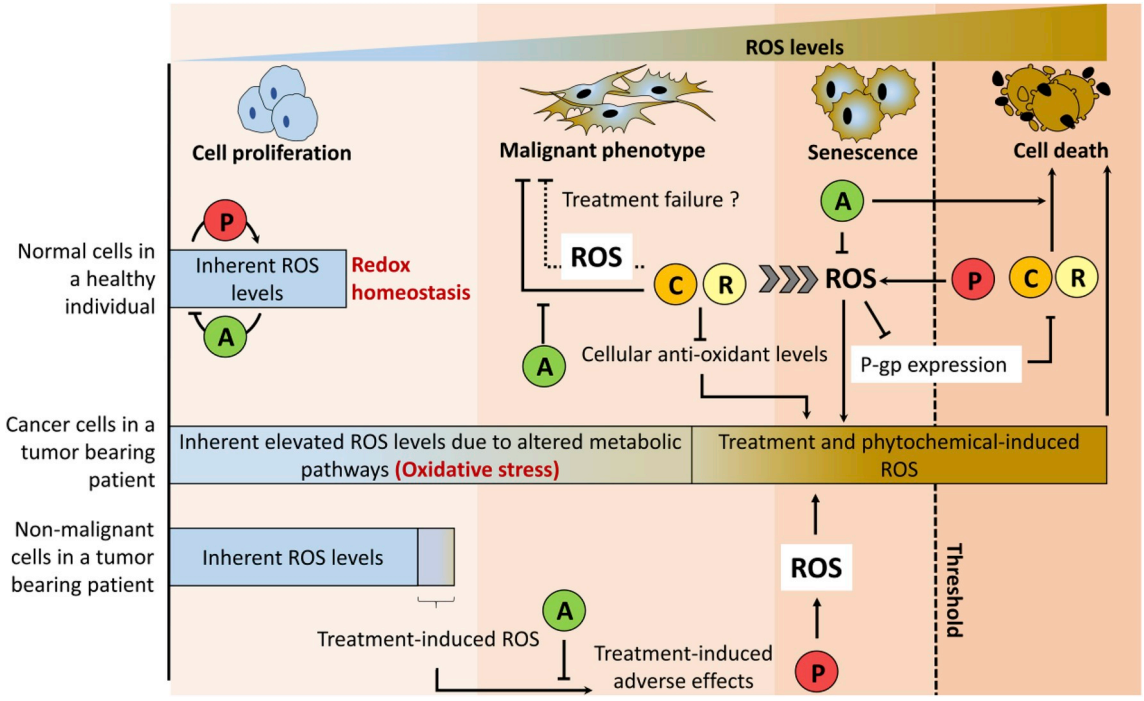

Fig. 5. A scheme for the impact of dietary anti-oxidants and pro-oxidants on the efficacy of ROS-dependent chemotherapy and radiotherapy. In normal healthy individuals, dietary anti-oxidants and pro-oxidants assist in the maintenance of redox homeostasis. Radiation treatment and chemotherapeutic drugs that induce intracellular ROS accumulation take advantage of the inherent differences in ROS levels between non-malignant and malignant cells in order to elicit selective toxicity toward malignant cells. However, cancer cells have the capacity to survive and maintain increased cell proliferation under conditions of oxidative stress. Since the selective cytotoxic activity of certain chemotherapeutic drugs and radiotherapy relies on the rapid rate of proliferation rate experienced by cancer cells, it is thought that concurrent anti-oxidant intake may desensitize cancer cells to these treatment modalities by decreasing ROS-dependent signaling that would otherwise maintain a high rate of cell proliferation rate. Thus, dietary anti-oxidants and pro-oxidants, by affecting intracellular ROS levels, may alter the effectiveness of radiation treatment and some forms of chemotherapy. **ROS**: reactive oxygen species; **A**: dietary anti-oxidants; **P**: dietary pro-oxidants; **C**: chemotherapy; **R**: radiotherapy.

that needs further consideration is the more accurate representation of "dietary" phytochemicals in *in vitro* studies. Single chemical entities isolated from or present in dietary sources are widely subjected to testing in *in vitro* assays; however, these studies do not accurately depict the enormous complexity of nutrient-rich dietary sources. The use of phytochemical mixtures in *in vitro* studies would provide more comprehensive answers to unsolved research questions. As a consequence of altered gene expression in cancer patients, the activity of transcription factors such as Nrf-2 involved in the expression of phase II drug metabolizing enzymes and drug efflux transporters are affected. Certain dietary phytochemicals found in fruits and vegetables largely tend to undergo first-pass phase II conjugation [152]; hence, the metabolic fate of those dietary phytochemicals differs between cancer patients and healthy individuals. The metabolism of phytochemicals in patients receiving chemotherapy or radiotherapy would, therefore, be more accurately mirrored in an animal model in which there is constitutive expression of Nrf-2. In conclusion, even though dietary phytochemicals with anti-cancer activities have been extensively studied, dietary phytochemicals with anti-oxidant and/or pro-oxidant activities should be consumed with caution by cancer patients until such time that more conclusive clinical data becomes available.

Conflicts of interest

The authors have no conflicts of interest to disclose.

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Appendix A. Supplementary data

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