Cancer Letters 413 (2018) 122–134

Contents lists available at ScienceDirect

Cancer Letters

journal homepage: www.elsevier.com/locate/canlet

Mini-review

Oxidative stress and dietary phytochemicals: Role in cancer chemoprevention and treatment

Shireen Chikara [a], Lokesh Dalasanur Nagaprashantha [a], Jyotsana Singhal [b], David Horne [b], Sanjay Awasthi [c], Sharad S. Singhal [a, *]

[a] Department of Medical Oncology, Beckman Research Institute of City of Hope, Comprehensive Cancer Center and National Medical Center, Duarte, CA 91010, USA
[b] Department of Molecular Medicine, Beckman Research Institute of City of Hope, Comprehensive Cancer Center and National Medical Center, Duarte, CA 91010, USA
[c] Department of Medical Oncology, Texas Tech University Health Sciences Center, Lubbock, TX 79430, USA

ARTICLE INFO

Article history:
Received 29 September 2017
Received in revised form
23 October 2017
Accepted 2 November 2017

Keywords:
Carcinogenesis
Chemoprevention
Chemotherapy
Oxidative stress
Nrf2
Phytochemicals

ABSTRACT

Several epidemiological observations have shown an inverse relation between consumption of plant-based foods, rich in phytochemicals, and incidence of cancer. Phytochemicals, secondary plant metabolites, *via* their antioxidant property play a key role in cancer chemoprevention by suppressing oxidative stress-induced DNA damage. In addition, they modulate several oxidative stress-mediated signaling pathways through their anti-oxidant effects, and ultimately protect cells from undergoing molecular changes that trigger carcinogenesis. In several instances, however, the pro-oxidant property of these phytochemicals has been observed with respect to cancer treatment. Further, *in vitro* and *in vivo* studies show that several phytochemicals potentiate the efficacy of chemotherapeutic agents by exacerbating oxidative stress in cancer cells. Therefore, we reviewed multiple studies investigating the role of dietary phytochemicals such as, curcumin (turmeric), epigallocatechin gallate (EGCG; green tea), resveratrol (grapes), phenethyl isothiocyanate (PEITC), sulforaphane (cruciferous vegetables), hesperidin, quercetin and 2′-hydroxyflavanone (2HF; citrus fruits) in regulating oxidative stress and associated signaling pathways in the context of cancer chemoprevention and treatment.

1. Introduction

Consumption of plant-based foods, such as fruits, vegetables, and whole grains, rich in diverse phytochemicals, secondary plant metabolites, is associated with positive health outcomes. Several case-control and epidemiological studies have reported an inverse relationship between intake of phytochemical-rich diet and incidence of breast [1,2], colon [3], lung [4,5], pancreas [6], and prostate

Abbreviations used: AKT, protein kinase B; AMPK, AMP-activated protein kinase; ARE, antioxidant response element; ATF-2, activating transcriptional factor; BBN, N-butyl-N-(4-hydroxybutyl)nitrosamine; CAF, cancer-associated fibroblasts; CDDP, cisplatin; CYPs, cytochrome P450s; COX-2, cyclooxygenase-2; CXCR4, chemokine receptor; DMBA, 7,12-dimethylbenz(*a*)anthracene; EGCG, epigallocatechin gallate; EMT, epithelial-to-mesenchymal transition; EpRE, electrophile response element; ERK, extracellular signal regulated kinase; γH2AX, phosphorylated H2AX; Glut-1, glucose transporter-1; GPx, glutathione peroxidase; GS-E, glutathione-electrophile conjugate; GSH, reduced glutathione; GS-HNE, GSH-4-hydroxy-*t*-2,3-nonenal conjugate; GSSG, oxidized glutathione; GST, glutathione-S-transferase; 2HF, 2′-hydroxyflavanone; 4-OHE2, 4-hydroxyestradiol; 4HNE, 4-hydroxynonenal; HGF, hepatocyte growth factor; Hh, hedgehog; H_2O_2, hydrogen peroxide; HMOX-1, heme oxygenase-1; ICAM-1, intercellular adhesion molecule-1; iNOS, inducible nitric oxide synthase; JAK, janus kinase; KEAP, kelch-like erythroid Cap'n'Collar homologue-associated protein; KRAS, kirsten rat sarcoma; MAOA, monoamine oxidase A; MAPK, mitogen activated protein kinase; MMP, matrix metalloproteinase; NAC, N-acetylcysteine; NFkB, nuclear factor-kappa B; 3NT, 3-nitrotyrosine; NNK, 4-(methylnitosamino)-1-(3-pyridyl)-1-butanone; ND6, NADH dehydrogenase subunit 6; NOX5, NADPH oxidase 5; NQO1, NAD(P)H: quinone oxidoreductase 1; Nrf2, nuclear factor-E2; NUDT1, nucleoside diphosphate linked moiety X-type motif 1; $OH^{\cdot}$, hydroxyl radicals; 8-OHdG, 8-oxo-2′-deoxyguanosine; $O_2^{\cdot}$, superoxide anion; OGG1, 8-oxoguanine DNA Glycosylase; PAH, polycyclic aromatic hydrocarbon; PEITC, phenethyl isothiocyanate; PhIP, 2-amino-1-methyl-6-phenylimidazo[4,5-*b*] pyridine; PARP, poly (ADP-ribose) polymerase; PI3K, phosphatidylinositol-3 kinase; PKC, protein kinase c; PMBC, peripheral blood mononuclear cells; PRDx, peroxiredoxins; QR, quinine reductase; RLIP76, ral-interacting protein; ROS, reactive oxygen species; siRNA, small-interfering RNA; SOD, superoxide dismutase; STAT, signal transducer and activator of transcription; TP53, tumor suppressor 53; TRXR, thioredoxin reductase; TXN, thioredoxins; uPA, urokinase-type plasminogen activator; UGT, UDP-glucuronosyltransferases.

* Corresponding author.
E-mail address: ssinghal@coh.org (S.S. Singhal).

https://doi.org/10.1016/j.canlet.2017.11.002
0304-3835/

[7,8] cancers. The cellular and molecular events regulated by these chemopreventive phytochemicals include apoptosis, cell cycle, cell proliferation, DNA repair, differentiation, carcinogen activation/detoxification by xenobiotic metabolizing enzymes, functional inactivation/activation of oncogenes and tumor-suppressor genes, angiogenesis, and metastasis. Along with these, mitigation of oxidative stress-mediated tumorigenesis is one of the mechanisms by which phytochemicals exert their anticancer potential (see Table 1).

Oxidative stress results from an imbalance in the production of reactive oxygen species (ROS) and the antioxidant capability of the cells [9]. ROS, such as, superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radicals ($OH^•$) are constantly produced in aerobic cells by incomplete reduction of molecular O_2 to H_2O during mitochondrial oxidative phosphorylation [9]. In addition, ROS are generated during a number of processes such as inflammation, infection, mechanical and chemical stresses, and exposure to UV-rays and ionizing radiation. Basal levels of ROS act as signaling molecules to activate cell proliferation, survival, apoptosis, differentiation, immune responses, motility, and stress-responsive pathways [10–12]. On the other hand, increased levels of ROS damage DNA, protein, and lipids which, if unrepaired, cause mutations and promote carcinogenesis [13]. However, excessive production of ROS results in extensive irreversible DNA damage, such as single or double-strand breaks, base modifications, and DNA cross links which ultimately leads to cell death [14,15]. Therefore, regulating cellular ROS is critical for maintaining cellular homeostasis.

A number of ROS-mediated signaling pathways, deregulation of which favors carcinogenesis, have been shown to be modulated by phytochemicals. In this article, we have primarily reviewed phytochemicals such as curcumin from turmeric, epigallocatechin gallate (EGCG) from green tea, resveratrol from grapes, phenethyl isothiocyanate (PEITC) and sulforaphane from cruciferous vegetables, hesperidin, 2′-hydroxyflavanone (2HF) and quercetin from citrus fruits in cancer chemoprevention. In addition, we have briefly reviewed the pro-oxidant properties of some of these phytochemicals, and their anticancer efficacy as an adjuvant chemotherapeutic agent in the context of cancer treatment.

2. Role of oxidative stress in carcinogenesis

Oxidative stress is associated with three stages of cancer development: initiation, promotion, and progression. The oxidative stress mediated mechanisms in carcinogenesis are represented in Fig. 1. During the initiation stage, oxidative stress leads to mutations in oncogenes and tumor-suppressor genes [16,17]. The 8-Hydroxy-2′-deoxyguanosine (8-OHdG) is a commonly observed oxidative stress-associated DNA-adduct. Elevated levels of 8-OHdG are noted in precancerous and cancerous tissues or cancer cell lines as compared to adjacent normal tissues or normal cell lines [18–22]. The presence of 8-OHdG results in GC to TA missense mutations, which if unrepaired prior to DNA replication, will produce a transformed cell (22). Interestingly, mutations in tumor suppressor (*TP53*) and oncogene (*KRAS*) observed in lungs of smokers exposed to tobacco smoke-induced oxidative stress are often related to the formation of 8-OHdG DNA-adducts [23,24].

The promotion stage, characterized by clonal expansion of transformed/initiated cells, may also be regulated by ROS. Oxidation of cysteine and methionine residues in proteins can affect their structure and enzymatic activities, resulting in deregulation of several signaling pathways, such as RAS-MEK-ERK1/2 [25], PI3K/AKT [26], Keap1-Nrf2-ARE [27], NFκB [28], and JAK/STAT [29]. An important group of proteins affected by ROS are phosphatases. Upon inactivation by ROS-mediated oxidation of the reactive cysteine thiol at their catalytic site, phosphatases are unable to dephosphorylate and thereby cannot inactivate target proteins, such as those belonging to RAS-MEK-ERK and PI3K/AKT signaling pathways, leading to their constitutive signaling and proliferation [30].

Finally, elevated levels of ROS contribute to progression phase of carcinogenesis by generating additional genomic instability that increases the metastatic potential of tumor cells. Cancer cells isolated from circulating blood and secondary tumor sites have been shown to display higher levels of cytoplasmic and mitochondrial-derived ROS than those from their primary tumors [31,32]. At the same time, mouse lung carcinoma cells having mutations in mitochondrial gene NADH dehydrogenase subunit 6 (*ND6*) showed higher ROS levels and increased metastatic potential compared to cells containing wild-type mitochondrial DNA [33]. Further, treatment with N-acetylcysteine (NAC), an antioxidant, abrogated the metastatic potential of these cells [33]. Indeed, a number of studies support the role of ROS in initiating tumor metastasis in animal models of breast [34], bladder [35], colon [36], lung [33], melanoma [37], and prostate [38] cancers. This has been attributed to ROS-mediated increased expression of matrix metalloproteinases (MMPs) which, *via* their proteolytic activities, assist in degradation of the extracellular matrix and basement membrane [35], aid in inhibition of an antioxidant enzyme catalase that detoxifies H_2O_2 [34], and stabilization of transcriptional factor HIF1α, a master regulator of O_2, which up-regulates vascular endothelial growth factor (VEGF) and stimulates angiogenesis [36,38].

In addition to ROS-mediated DNA damage, lipid peroxidation in the presence of high ROS level plays a critical role in carcinogenesis. Generally, the cellular concentration of 4-hydroxynonenal (4HNE), a major end products of lipid peroxidation, ranges from 0.1 to 0.3 mM, however, during oxidative stress, it may increase by several folds [39]. It has been estimated that 1–8% of the 4HNE may form protein adducts [40], of which about 30% are located in mitochondria and are members of electron transport chain [41]. In addition, in liver carcinoma, 4HNE has been shown to form mutagenic DNA-adducts in *TP53* [42]. Further, 4HNE protein adducts in renal and colon cancer tissues have been shown to promote growth and progression of kidney and colon cancers [43]. Therefore, production of lipid-derived radicals can interact and modify proteins and DNA to further aggravate oxidative stress and promote carcinogenesis.

3. Oxidative stress and antioxidant defense mechanism

3.1. Nrf2-ARE pathway

Nuclear factor-E2 related factor 2 (Nrf2) is a transcription factor that binds to the antioxidant response element (ARE) in the 5′-flanking region of antioxidant and detoxification genes in response to oxidative stress [44]. The cancer protective role of Nrf2 is evident in *Nrf2*-knockout (−/−) mice which are highly susceptible to carcinogen-induced gastric neoplasia [45], and inflammation-induced colon carcinogenesis [46]. Under normal conditions, a majority of the Nrf2 is sequestered in the cytoplasm by Kelch-like erythroid Cap'n'Collar homologue-associated protein 1 (Keap 1) [47], and only residual nuclear Nrf2 binds to the ARE, and drives basal expression of target genes. These target genes that neutralize ROS include superoxide dismutases (*SODs*), catalase, heme oxygenase-1 (*HMOX-1*), glutathione peroxidase (*GPx*), thioredoxins (*TXN*), thioredoxin reductase (*TRXR*), peroxiredoxins (*PRDx*), NAD(P)H: quinone oxidoreductase 1 (*NQO1*), and glutathione-S-transferase (*GSTs*) (Fig. 2) [48]. For example, SOD converts O_2^- to O_2 or H_2O_2 and catalase and GPx convert H_2O_2 to H_2O and O_2 [49]. In addition, the endogenous non-enzymatic antioxidants include