

Unifying Mechanism for Nutrients as Anticancer Agents: Electron Transfer, Reactive Oxygen Species and Oxidative Stress

Peter Kovacic¹ & Ratnasamy Somanathan²

¹ Department of Chemistry and Biochemistry, San Diego State University, San Diego, CA 92182-1030, USA

² Centro de Graduados e Investigación del Instituto Tecnológico de Tijuana, Apdo, Tijuana, B.C. Mexico

Correspondence: Ratnasamy Somanathan, Centro de Graduados e Investigación del Instituto Tecnológico de Tijuana, Apdo. postal 1166, Tijuana, B.C. Mexico. E-mail: rsoamanathan@mail.sdsu.edu

Received: March 13, 2017 Accepted: May 16, 2017 Online Published: May 29, 2017

doi:10.5539/gjhs.v9n8p66

URL: <https://doi.org/10.5539/gjhs.v9n8p66>

Abstract

A recent article deals with various nutrients in relation to bactericidal action. The present article focuses on a unifying mode of action for the nutrients, namely, resveratrol, epigallocatechin, polyene- β -carotene, polyene lycopene, piperine, curcumin, genistein, luteolin, sulforaphane and pomegranate extract. The mechanism is based on electron transfer, reactive oxygen species and oxidative stress, which comprises an extension of earlier reports involving agents. Most of the compounds are precursors of electron transfer quinones, whereas others fit into the polyene category. The nutrients are better known as antioxidants. The dichotomy is addressed.

Keywords: nutrients, cancer stem cells, anticancer, electron transfer, radicals, oxidative stress, reactive oxygen species

Abbreviations

ROS=Reactive oxygen species

OS= oxidative stress

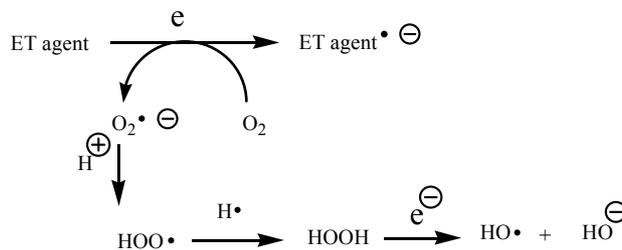
RNS= reactive nitrogen species

ET= electron transfer

1. Introduction

Anticancer drugs are often synthetic agents originally derived from plants. Recently an article reported anticancer activity by diet nutrients, namely, resveratrol, epigallocatechin, polyene- β -carotene, polyene lycopene, piperine, curcumin, genistein, luteolin, sulforaphane and pomegranate extract (Scarpa & Ninfali, 2015). Mode of action was attributed to cell signaling involving cancer stem cells. In 2007, a unifying mechanism for anticancer action was proposed as discussed below (Kovacic, 2007). The nutrients fit into the unifying mechanism which has been widely applied previously as set forth as follows (Kovacic & Somanathan, 2010).

“The preponderance of bioactive substances, usually as the metabolites, incorporate ET functionalities. We believe these ET-metabolites play an important role in physiological responses. The main group include quinones (or phenolic precursors), metal complexes (or complexors), aromatic nitro compounds (or reduced hydroxylamine and nitroso derivatives), and conjugated imines (or iminium species). Resultant redox cycling is illustrated in Scheme 1. In vivo redox cycling with oxygen can occur, giving rise to oxidative stress (OS) through generation of reactive oxygen species (ROS), such as hydrogen peroxide, hydroperoxides, alkyl peroxides, and diverse radicals (hydroxyl, alkoxy, hydroperoxy, and superoxide) (Scheme 1). Cellular and mitochondrial enzymes can also perform catalytically in the reduction of O₂.



Scheme 1. Redox cycling with superoxide and ROS formation.

In some cases ET results in involvement with normal electrical effects (e.g., in respiration or neurochemistry). Generally, active entities possessing ET groups display reduction potentials in the physiologically responsive range, (i.e., more positive than about -0.5 V). Hence, ET *in vivo* can occur resulting in production of ROS which can be beneficial in cell signaling at low concentrations, but produce toxic results at high levels. Electron donors consist of phenols, N-heterocycles or disulfides in proteins which produce relatively stable radical cations. ET, ROS and OS have been increasingly implicated in the mode of action of drugs and toxins, e.g., anti-infective agents (Kovacic & Becvar, 2000), anticancer drugs (Kovacic & Osuna, 2000), carcinogens (Kovacic & Jacintho, 2001a), reproductive toxins (Kovacic & Jacintho, 2001b), nephrotoxins (Kocavbic, Sacman, & Wu-Weis, 2002), hepatotoxins (Poli, Cheeseman, Dianzani & Slater, 1989), cardiovascular toxins (Kovacic & Thurn, 2005), nerve toxins (Kovacic & Somanathan, 2005), mitochondrial toxins (Kovacic, Pozos, Somanathan, Shangari, & O'Brien, 2005), abused drugs (Kovacic & Cooksy, 2005), pulmonary toxins (Kovacic & Somanathan, 2009), ototoxins (Kovacic & Somanathan, 2008) and various other categories (Halliwell & Gutteridge, 1999).

There is a plethora of experimental evidence supporting the ET-ROS theoretical framework (Kovacic & Becvar, 2000; Kovacic & Osuna, 2000; Kovacic & Jacintho, 2001a; Kovacic & Jacintho, 2001b; Kovacic, Sacman & Wu-Weis, 2002; Poli, Cheeseman, Dianzani, & Slater, 1989; Kovacic & Thurn, 2005; Kovacic & Somanathan, 2005; Kovacic, Pozos, Somanathan, Shangari, & O'Brien, 2005; Kovacic & Cooksy, 2005; Kovacic & Somanathan, 2009; Kovacic & Somanathan, 2008; Halliwell & Gutteridge, 1999). This evidence includes generation of the common ROS, lipid peroxidation, degradation products of oxidation, depletion of AOs, effect of exogenous AOs, and DNA oxidation and cleavage products, as well as electrochemical data. This comprehensive, unifying mechanism is consistent with the frequent observation that many ET substances display a variety of activities (e.g., multiple-drug properties), as well as toxic effects.

It is important to recognize that mode of action in the bio domain is often involved with many physiological actions and is multifaceted. In addition to the ET-ROS-OS approach, other aspects may pertain, such as, enzyme inhibition, allosteric effects, receptor binding, metabolism and physical factors. A specific example involves protein binding by quinones in which protein and nucleophiles, such as amino or thiol, effect conjugate addition.”

As indicated above, focus is on ROS-OS in relation to mechanism. However, most attention in the literature is paid to AO action in relation to physiological action, but is of little importance in the present case. An example is discussed with β -carotene.

2. ROS and Cancer

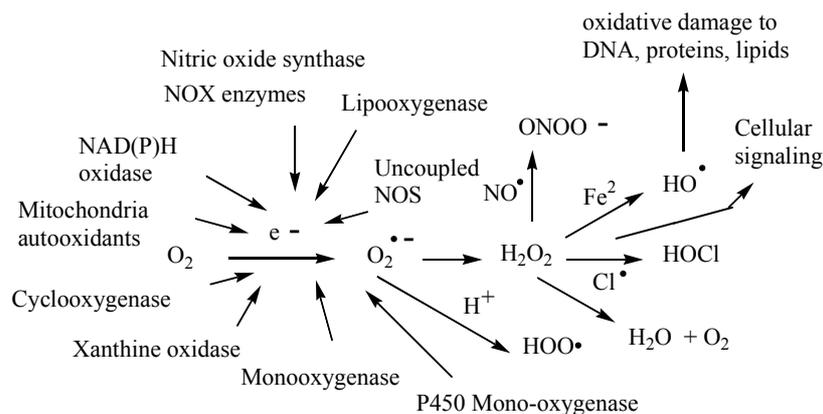
In recent years, a large body of literature has emerged documenting the link between ROS, reactive nitrogen species (RNS), OS and ET and cancer (Liou & Storz, 2010; Sullivan & Chandel, 2014; Halliwell, 2001).

Reactive oxygen species are radicals, ions or molecules that have unpaired electrons. They can be classified into two groups: free oxygen radicals and non-radical ROS (Table 1). Among these, superoxide, hydrogen peroxide and hydroxyl radicals are the most potent and well studied species. The roles of reactive oxygen species in tumorigenesis, prevention, and therapy has been discussed in more recent reviews (Liou & Storz, 2010; Sullivan & Chandel, 2014; Halliwell, 2001; Kovacic & Jacintho, 2001a; Gupta, Hevia, Patchva, Park, Koh, & Aggarwal, 2012).

Table 1. Reactive oxygen and nitrogen species

| Radical ROS | | Non-radical ROS | |
|------------------|-----------------|-----------------------|----------|
| Superoxide | $O_2^{\cdot -}$ | Hydrogen peroxide | H_2O_2 |
| Hydroxyl radical | $OH\cdot$ | Singlet oxygen | O_2 |
| Nitric oxide | $NHO\cdot$ | Ozone | O_3 |
| Organic radicals | $R\cdot$ | Hypochlorous acid | $HOCl$ |
| Peroxyl radicals | $ROO\cdot$ | Organic hydroperoxide | $ROOH$ |
| Alkoxy radicals | ROH | Peroxynitrite | $ONOH^-$ |
| Nitrogen dioxide | NO_2 | Nitrous acid | HNO_2 |

A variety of enzymatic and non-enzymatic sources of ROS exists in the biological system. Enzymes within the cell are primary sources of ROS/RNS. Superoxide is produced by one electron reduction of oxygen by several enzymes, such as NAD(P)H oxidase, xanthine oxidase and cytochrome P450 within the cell. In addition to these, a number of external mediators also contribute to the ROS generation, such as ionizing radiation. Heavy metals, like Hg, Pb, Cd, Cr, and Cu, metal complexes, nano particles, cigarette smoke, pollutants from automobiles, fossil burning furnaces, various drugs and certain types of other chemical compounds (Scheme 1) play a role. In cancer affected cells, high levels of ROS can result from mitochondrial dysfunction, high metabolic activity, cellular signaling, peroxisome activity, oncogene activity, oxidase activity, cyclooxygenase and lipoxigenase activity (Liou & Storz, 2010; Sullivan & Chandel, 2014; Halliwell, 2001).



Scheme 1. Generation of ROS

In mitochondria, superoxide ROS is produced as a natural by-product of electron transport chain activity (Cui, Reichner, Mateo, & Albino, 1994). The superoxide leaks through the mitochondrial permeability transition pore in the outer membrane into the cytoplasm, where it is dismutated into hydrogen peroxide by MnSOD or in the cytosol by Cu/ZnSOD. The diffusible hydrogen peroxide also serves as a second messenger, and may cross cellular membranes through members of the aquaporin family (Scarpa & Ninfali, 2015). Cancers arise from sites of chronic irritation, or inflammation and play a critical role in tumor progression (Liou & Storz, 2010). Within the cancer cells, macrophages produce ROS which kill the tumor cells. This production of superoxide, hydroxyl radical, hydrogen peroxide, nitric oxide and peroxynitrite radicals contributes to tumor cell apoptosis (Liou & Storz, 2010; Cui, Reichner, Mateo, & Albino, 1994).

A 2012 review deals with ROS as initiators of cancer and also as therapy in destroying the cells (Cui, Reichner, Mateo, & Albino, 1994). The review highlights: a) ROS play an important role in the initiation and progression of

cancer; b) cancer cells exhibit greater ROS stress than normal cells, due to increased metabolic activity and mitochondrial dysfunction; c) cell-cycle progression is dependent on tyrosine kinase, which in turn depends on ROS; d) chronic inflammation due to cancer is mediated by ROS; e) ROS controls tumor expression genes, such as p53; and f) ROS can also suppress tumor growth. As a result of these accumulated data, a number of pro-oxidant and antioxidant based anticancer agents have been developed. Many of these approved drugs do show promise in suppressing cancer growth. However, a majority of the chemotherapeutic drugs shrink tumor size, but often fail to eradicate tumors.

2.1 Cancer Stem Cells and Epithelial-Mesenchymal Transition Cells

In the past decade, research has provided strong support for the theory of cancer stem cells (CSC) or tumor-initiating cells (TICs) involved in several human cancers (Aziz & Wicha, 2013; Matchett & Lappin; Enderling, 2015; Schukenburg, Blatt, Cerny-Reiterer, Sadovnik et al., 2014; Fulawka, Donizy, & Halon, 2014; Kreso & Dick, 2014; Oskarsson, Batlle, & Massague, 2014; Lobo, Shimono, Qian, & Clark, 2007). The hypothesis states that cancer cells arise in self-renewing cell populations and that the resulting cancers, like their normal organ counterparts, are composed of hierarchically organized cell population (Aziz & Wicha, 2013). Self-renewing cancer cells maintain tumor growth and generate the diverse populations constituting the tumor bulk. Recently, epithelial-mesenchymal transition (EMT), a process that is reminiscent of that in cancer stem cells, along with ROS, has been associated with tumor metastasis, tumor cell migration, invasion and angiogenesis (Wang, Li, & Sarkar, 2010; Diehn, Cho, Lobo, Kalisky et al., 2009). A current research focus is to develop therapy to suppress renewal of cancer stem cells by inhibiting the following signaling pathways, Hedgehog, Notch, Wnt, CXCR4, FOXM1, and miRNAs (Xia et al., 2012; Liu, Dontu, & Wicha, 2005; Korkaya, Paulson, Charaf-Jauffret et al., 2009; Liu, Dontu, & Mantle, 2006; Reya, Morrison, Clarke, & Weissman, 2001; Dontu, Jackson, McNicholas, et al., 2004; Smally & Dale, 1999; Clevers, 2006; Liu, Semenov, Han et al., 2002).

2.2 Cancer Stem Cells and Natural Dietary Compounds

The emergence of cancer stem theory has profound implications for cancer chemoprevention and therapy. Recently, studies have found that several dietary compounds can directly or indirectly affect cancer stem cells pathways (Li, Wicha, Schwartz, & Sun, 2011; Lee, Huang, & Shyur, 2013; Khan, Adhami, & Mukhtar, 2008). The dietary compounds, including resveratrol, epigallocatechin, polyene- β -carotene, polynene lycopene, piperine, curcumin, sulforaphane, soy isoflavone genistein, and vitamin D₃, are known to effect directly or indirectly the self-renewable pathways (Li, Wicha, Schwartz, & Sun, 2011). So far, several major pathways including Wnt/ β -catenin, Hedgehog, and Notch have been identified as playing pivotal roles in CSC self-renewal (Liu, Dontu, & Mantle, 2006; Smally & Dale, 1999; Dontu, Jackson, McNicholas et al., 2004).

3. Curcumin

Curcumin (diferuloylmethane) (Figure 1) is one of the active components of dietary spice turmeric (*Curcuma longa*, Linn) which is used in the preparation of curry, an East Indian dish. Curcumin possesses anti-inflammatory and antioxidant activities, and has been studied as a chemoprevention agent in several cancer models (Li, Wicha, Schwartz, & Sun, 2011; Rahmani, Al Zohairy, Aly, & Khan, 2014; Attari, Zahmatkesh, Aligholi et al., 2015; Gupta, Kismali, & Agarwal, 2013) (Figure 1).

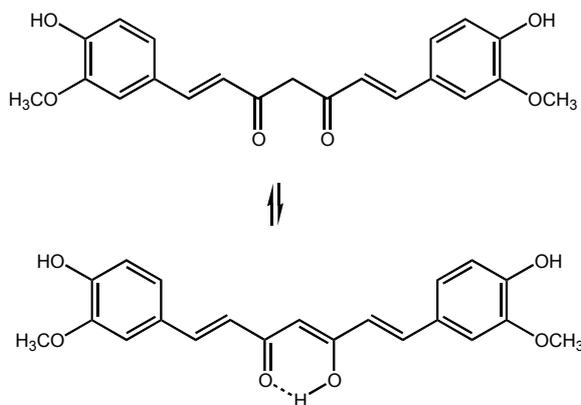


Figure 1. Curcumin

In relation to the unifying mechanistic approach, metabolism may yield a catechol type which lead to o-quinone or p-quinone structures, followed by ROS-OS (Kovacic & Somanathan, 2015). Study reveals curcumin (Figure 1) induced caspase-3-mediated cleavage of β -catenin, leading to inactivation of Wnt/ β -catenin signaling in intestinal, gastric, and colon cancer cells (Park, Hahm, Park et al., 2005; Jaiswal, Marlow, Gupta, & Narayan, 2002; Ramasamy, Ayob, Myint et al., 2015). Curcumin was also shown to attenuate the Wnt/ β -catenin pathway through down-regulation of the transcriptional coactivator p300 (Ryu, Cho, & Song, 2008). A related study showed curcumin inhibits breast cancer stem cell migration by amplifying the E-cadherin/ β -catenin feedback loop (Mukherjee, Mazumdar, Chakraborty et al., 2014). Kakarala and coworkers showed curcumin inhibits Wnt signaling in breast cancer stem cell self renewal, but do not cause toxicity to differential cells (Kakaral, Brenner, Khorkaya et al., 2010). A similar study revealed curcumin has little toxicity against normal stem cells compared to cancer stem cells (Sordillo & Helson, 2015). The phenol down regulates Notch-1 level with inhibition of cell growth and induction of apoptosis in pancreatic cancer cells (Wang, Zhang, Banerjee et al., 2006). Curcumin and epigallocatechin gallate combined specifically to inhibit STAT3 phosphorylation and STAT3-NF κ B interaction was retained in breast cancer stem cells (Chung & Vadgama, 2015). It has been demonstrated that curcumin can eliminate cancer stem cells in various human cancers (Yu, Kanwar, Patel et al., 2009; Lin, Liu, Li et al., 2011; Lim, Bisht, Bar et al., 2011). Yu and coworkers reported that the agent by itself or with other chemotherapeutics can prevent renewal of chemo resistant colon CSCs through the activation of STAT3 (signal transducer and activator of transcription) (Kovacic & Somanathan, 2005; Kovacic, Pozos, Somanathan et al., 2005). A study by Lim and coworkers revealed that curcumin-nanoparticles can inhibit malignant brain tumor growth by controlling stem cell proliferation through STAT3 and Hedgehog pathway (Kovacic & Cooks, 2005).

4. Genistein

Genistein (Figure 2), an isoflavone, is the active ingredient in soya-rich food.

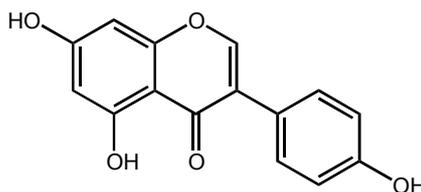


Figure 2. Genistein

Studies show that genistein and high soya-food consumption have been associated with reduced risk of breast and other forms of cancer among Asian Americans (Ziegler, Hoover, Pike et al., 1993; Iwasaki, Inoue, Otani et al., 2008; Verheus, Van Gils, Keinan-Boker et al., 2007; Barnes, 1995). Long term, low dose genistein consumption decreases stem cell population and sensitizes inflammatory breast cancer cell lines to radiation (Sims-Moutada, Opdenaker, Davis, & Wu, 2015). A report deals with genistein as a dietary phytochemical target in human prostate cancer stem cells (Zhang, Li, Jiao et al., 2012). The phenol suppressed tumorsphere and colony formation of prostate cancer cells by inhibiting Hedgehog-Gli1 pathway. Genistein inhibited breast cancer cell growth, proliferation and promoted apoptosis (Fan, Fan, Wang et al., 2013). Genistein decreased breast cancer stem cells by inhibiting cancer stem cells by down regulating Hedgehog-Gli1 signaling pathway. Gli1 expression was inhibited, resulting in the attenuation of cancer stem like properties in gastric cancer cells (Yu, Shin, Lee et al., 2014). In addition, genistein suppresses the cell invasive capacity that is required for tumor growth and metastasis. A study showed inhibition by the phenol of β -catenin –mediated WNT signaling through gene expression by demethylating its silenced promoter in colon cancer cell lines (Zhang & Chen, 2011). A similar study with renal cancer cells also showed inhibition of Wnt-signaling, thus effecting the proliferation and renewal of cancer stem cells (Hirata, Ueno, Nakajima et al., 2013). Data showed genistein, a natural chemo-preventive agent, inhibited cell growth, clonogenicity, cell migration and invasion, epithelial-mesenchymal transition, cancer stem cell phenotype, and formation of pancreatospheres in pancreatic cancer cells (Bao, Wang, Ali et al., 2011; Bao, Wang, Ali et al., 2011). A novel isoflavone NV-128, significantly targeted mitochondria to induce cell death in chemo-resistant ovarian cancer stem cells (Alvero, Montagna, Holmberg et al., 2011). The phenol protects hematopoietic stem cells against granulocyte colony-stimulating factor (G-CSF)-induced DNA damage (Souza, Silva, Calloway et al., 2014). There is ample precedent for metabolism entailing phenolic oxidation followed by conversion to catechol or hydroquinone type with subsequent oxidation to quinone followed by generation of ROS-OS.

5. Luteolin

Luteolin, 3',4',5,7-tetrahydroxyflavone (Figure 3), is a common flavonoid that exists in many types of plants including fruits, vegetables, and medicinal herbs. Plants rich in luteolin have been used in Chinese traditional medicine for treating diseases, such as hypertension, inflammatory disorders, and cancer. Having multiple biological effects, the phenol functions as an antioxidant and as well as a pro-oxidant biochemically (Lin, Anxin Shi, Wang, & Shen, 2008).

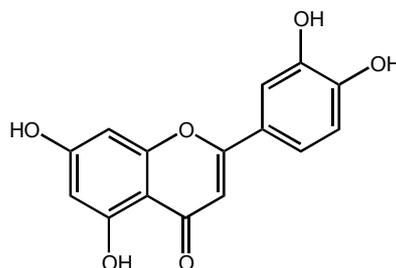


Figure 3. Luteolin

Two 2008 reviews deal with the luteolin's anticancer property with the induction of apoptosis, inhibition of cell proliferation, metastasis and angiogenesis (Lin, Anxin Shi, Wang & Shen, 2008; Seelinger, Merfort et al., 2008). Furthermore, luteolin sensitizes cancer cells to therapeutic-induced cytotoxicity through suppressing cell survival pathways, such as phosphatidylinositol 3'-kinase/Akt, nuclear factor kappa B (NF- κ B) (Yang, Cai, Yang et al., 2014), and X-linked inhibitor of apoptosis protein, and stimulating apoptosis pathways including those that induce the tumor suppressor p53. Data suggest luteolin could be an anticancer agent for various cancers (Scarpa & Ninfali, 2015). Luteolin induced ROS acts as potential cytotoxic agent to human colorectal cell line (Pandurangan & Ganapasam, 2013; Pandurangam, Sadagopan et al., 2013).

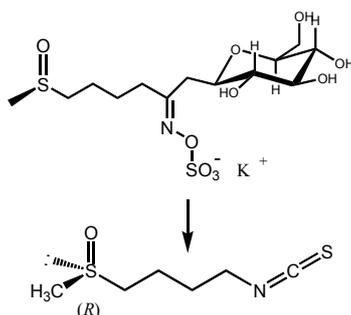
A study showed luteolin inhibits RNAs (RSK) and eradicates the CSC population (Davis, REipas, Hu et al., 2015). It effectively blocks progesterin-dependent human breast cancer tumor growth and stem cell-like phenotype in human breast cancer (Cook, Liang, Besch-Williford et al., 2015). A similar study revealed retardation of growth by MCF-7 cells via inhibiting insulin growth factor (IGF-1) mediated PI3K-Akt pathway dependent ER α in human breast cancer stem cells (Wang, Xie, Huo et al., 2012).

Luteolin inhibits the hypoxia-induced EMT in malignant melanoma cells both in vitro and in vivo via the regulation of β 3 integrin, suggesting action as a potential anticancer chemo preventive and chemotherapeutic agent (Ruan, Liu, Zhang et al., 2012). Luteolin induces apoptosis in multidrug resistant cancer cells via ROS generation, DNA damage, activation of p53, NF- κ B signaling pathways, activation of p38 pathway and depletion of anti-apoptotic proteins (Rao, Satelli, Moridani et al., 2011). Glioma is one of the most common malignant tumors affecting the central nervous system. Drug screening using curcumin, luteolin, chrysin and apigenin, showed suppression of the tumor cells (Feng, Zhou, Liu, & Tao, 2012).

6. Sulforaphane

Broccoli and broccoli sprouts contain large amounts of glucosinolates. Numerous studies have substantiated the chemopreventive properties of cruciferous vegetables against cancer, which has been attributed to the activity of various isothiocyanates that are enzymatically hydrolyzed from glucosinolates. Sulforaphane is formed from glucoraphanin, a major glucosinolate in broccoli/broccoli sprouts by enzymatic hydrolysis (Clarke, Dashwood & Ho, 2008; Fahey, Zhang, & Talalay 1997) (Scheme-3). A study revealed the naturally occurring (*R*) – isomer is more effective than the synthetic (*S*)-isomer in a study of quinone reductase and glutathione S-transferase activities (Scarpa & Ninfali, 2015). Sulforaphane inhibits enzymes that convert procarcinogens to carcinogens, promote excretion of carcinogens, affect growth of transformed cells, induces apoptosis and cell cycle arrest (Li, Zhang, Korkaya et al., 2010). Accumulating evidence showed sulforaphane inhibits breast cancer stem cells (Liu, Dontu, & Wicha, 2005; Korkaya, Paulson, Charaf-Jauffret et al., 2009), and targets pancreatic tumor-initiating cells by NF- κ B-induced antiapoptotic signaling (Kallifatidis, Rausch, Baumann et al., 2009). The compound was shown to target CSCs in different cancer through modulation of NF- κ B, sonic hedgehog, epithelial-mesenchymal transition and Wnt/ β -catenin pathways (Li & Zhang, 2013). A related study showed targeting of sonic hedgehog signaling inhibition in pancreatic and prostate stem cell self-renewal (Rodova, Fu, Watkins et al., 2012; Kallifatidis, Labsch, Rausch et al., 2011). An investigation showed sulforaphane eliminated breast CSCs in vivo, by activation of

caspase-3 (Li, Zhang, Korkaya et al., 2010; Park, Lim, Bae et al., 2007). A related study showed sulforaphane-induced apoptosis of human breast cancer cell involving PKC β -mediated S36 phosphorylation of p66^{shc} (Sako & Singh, 2012). The isocyanate along with vitamin D shows greater down-regulation of the Wnt-signaling pathway (Lee, Yang, & Liu, 2015). Sulforaphane and human tumor necrosis factor TNF-related apoptosis ligand (TRAIL) induce synergistic elimination of advanced prostate cancer-stem-like cells (Labsch, Bauer, Zhang et al., 2014). Mediated cleavage of Notch isoforms led to the inhibition of human prostate cancer cell migration (Hahm, Chandra-Kuntal, Desai et al., 2012). Data showed sulforaphane synergizes with quercetin to inhibit self-renewal capacity of pancreatic cancer stem cells by inhibiting the expression of Bcl-2 and XIAP, phosphorylation of FKFR, and activating caspase-3 (Srivastava, Tang, Zhu et al. 2011).



Scheme 3. Formation of sulforaphane from glucosinolate

7. Pomegranate Extract

Historically pomegranate (*Punica granatum L*), has been used as a medicine for variety of ailments in various cultures. In studies of human and murine models, pomegranate juice, peel, and oil have shown to possess anticancer activities, including interference with tumor cell proliferation, cell cycle, invasion, angiogenesis, anti-inflammatory, antiatherogenic, and antioxidant activities (Bhandari, 2012; Sudhakar, Venugopal, & Karthikaeyan, 2015; Tuurini, Ferruzzi, & Filmognari, 2015).

The peel of pomegranate possesses a higher content of polyphenols. The fruit contains large amounts of ellagic acid and its derivatives (Figure 4), along with punicalagin (Figure 6), a large polyphenol being the major constituent, possesses >50% of the antioxidant activity of pomegranate juice. Pomegranate also contains other polyphenols, such as anthocyanins, cyanidin (Figure 5), caffeic acid, coumaric acid and flavonols. Ellagic acid is metabolized by the colon microflora to form urolithins A and B that circulate in the blood stream reaching various organs, playing a role as antioxidants, anti-inflammatory and anticancerous agents (Sudhakar, Venugopal, & Karthikaeyan, 2015). Four recent reviews deal with the role of pomegranate juice in breast cancer, colon cancer, pancreatic cancer, hepatocellular carcinoma, prostate cancer and human larynx epidermal carcinoma (Bhandari, 2012; Sudhakar, Venugopal & Karthikaeyan, 2015; Tuurini, Ferruzzi, & Filmognari, 2015). Mechanistically, as discussed in prior sections, the catechol can act as o-quinone precursor leading to ET-ROS-OS as part of the unifying theme.

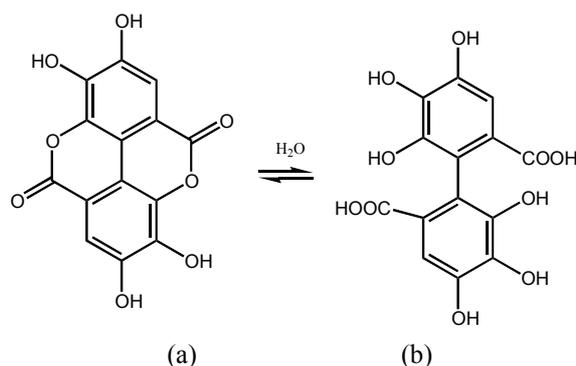


Figure 4. Ellagic acid (a) and hydrolysis product (b)

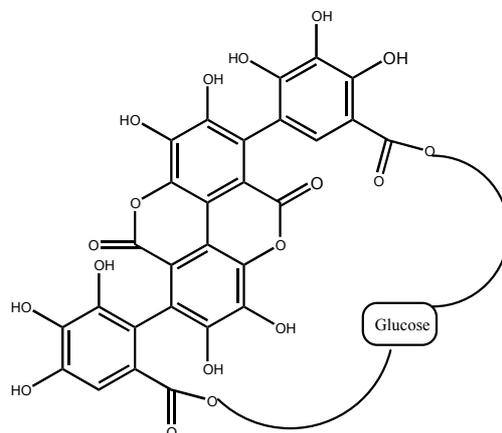


Figure 5. Punicalgin

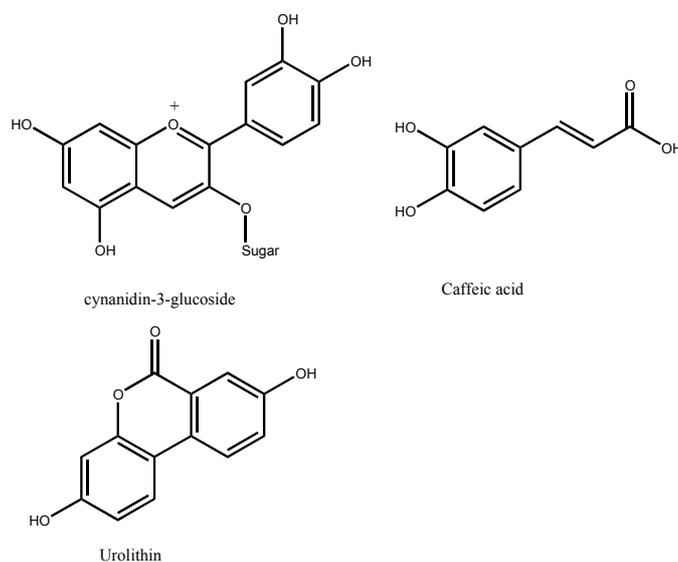


Figure 6. Polyphenols

8. Resveratrol (RSV)

There is considerable literature that documents RSV (Figure 7) as a pro-oxidant, which is in accord with the unifying theme of ET-ROS-OS (Kovacic & Somanathan, 2010). Compounds related to RSV display oxidative properties (Miura, Muraoka, & Fujimoto, 2002). Conditions are important for DNA oxidation leading to apoptosis (Athar, Back, Kopelovich et al., 2009). A study revealed formation of superoxide (Ahmad, Clement, & Pervaiz, 2003). In the dark, AO properties prevail whereas under light exposure, oxidative effects are predominant (Gadacha, ben-Attia, Bonfont et al., 2009). Another rationale exists for the pro-oxidant effects based on complex formation with heavier metals capable of ET (see Introduction). This route is more favorable for catechol types.

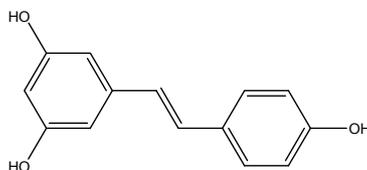


Figure 7. Resveratrol

Relevant research literature has been published in the last five years. RSV is similar to chemotherapeutic drugs in relation to DNA damage (Colin, Limagne, Ragot et al., 2014). The insult was the result of large scale generation of ROS. The results are rationalized in the Introduction involving oxidation of RSV to a catechol type followed by oxidative conversion to an o-quinone leading to ET and ROS-OS.

Exposure to RSV and histone deacetylase inhibitors resulted in prolonged ROS generation with subsequent DNA cleavage (Yasen, Chen, Hock et al., 2012). A free radical scavenger hindered production of ROS, DNA damage and apoptosis, indicating an important role for oxidative insult.

RSV together with UVA produces pronounced OS in mitochondria which leads to apoptosis in keratinocytes (Yar, Menevse, Dogan et al., 2012). These findings may have practical application in treatment of skin cancer. The polyphenol is known to act as an antitumor agent and in chemoprevention (Stocco, Toledo, Salvador et al., 2012). High concentrations were needed to induce death of cancer cells. Exposure to RSV resulted in apoptosis and DNA damage in human gastric cancer cells via ROS (Wang, Li, Meng, & Jia, 2012). Exposure of the cells to SOD or catalase countered apoptosis by destroying ROS. In a report on colorectal cancer, RSV interacted with mitochondria resulting in enhancement of ROS and lipid peroxidation (Zhou, Chen, Yang et al., 2014). Combination of RSV with 5-fluorouracil resulted in enhanced OS. Arsenic trioxide is a powerful anticancer drug for treatment of leukemia (Gu, Chen, Jiang, & Zhang, 2015). The combination of RSV and arsenite increased apoptotic cancer cell death through generation of OS. A report deals with OS in eye cells of diabetic rats involving an increase in OS (Boyer, Jandova, Janda et al., 2012). Protein carbonyl content was increased and GSH levels were decreased. We suggest a result of ROS-OS.

A study was made of a related derivative, 3,3',4,4'-tetrahydroxy-trans-stilbene (Mikula-Pietrasik, Sosinka et al., 2015). In cancer cells, drug treatment resulted in increased generation of ROS and catalase. Cytotoxicity was related to enhanced apoptosis. There also was formation of 8-OH-2'-dG resulting from DNA oxidation. Higher hydroxylated analogs of RSV display both pro-oxidant and AO effects (Kucinska, Piotrowska, Luczak et al., 2014). Pro-oxidant activity is attributed to cytotoxicity and apoptotic effects. Cell death occurred along with OS and decrease in GSH and SOD (Santandreu, Valle, Oliver, & Roca, 2011). Cytotoxicity may be related to generation of pro-oxidative metabolites. The following phenolic derivatives of trans-stilbene were involved: 3,3',4,4'-tetrahydroxy, 3,4,4',5-tetrahydroxy and 3,3',4,4',5,5'-hexahydroxy. These phenols can act as precursors of quinones which enter into ET-ROS-OS (see Introduction).

9. Epigallocatechin gallate (EGCG)

EGCG (Fig. 8) is a polyphenol prevalent in green tea (Scarpa & Ninfali, 2015). Clinical trials comprise the phenol alone or together with platinum (Pt) drugs involving synergism against prostate and colon cancers. One mode of action entails induction of apoptosis in tumor cells and animal models, which can result from OS (Halliwell & Gutteridge, 1999). Increase in ROS occurs during gallate-induced apoptosis of hepatic cancer cells (Li, Nie, Yu, & Xie, 2009). The compound enhanced the production of radicals, both ROS and RNS (Jeong, Park, Cho et al., 2015). A study was made of the drug effect on Leishmania (Inacio, Gervazoni, Canto-Cavalheiro et al., 2014). Results suggest a mode of action involving ROS. The effect was reversed by catalase, providing evidence for ROS involvement.

In relation to the ET-ROS-OS unifying mechanism, the catechol portion can act as precursor of an o-quinone which is an ET agent capable of inducing ROS-OS which plays a role in cancer destruction.

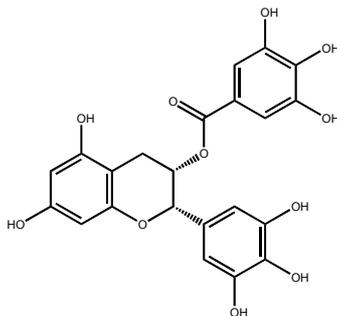


Figure 8. Epigallocatechin gallate

10. Piperine

Piperine (Figure 9) is an alkaloid which produces the pungency of pepper. Various mechanisms have been advanced in connection with bioactivity. The compound activates ions associated with pain-sensing nerve cells (McNamara, Randall, & Gunthorpe, 2005), and also inhibits enzymes involved with metabolism of xenobiotics (Bhardwaj, Glaser, Becquemont et al., 2002; Srinivasan, 2007), of drugs (Atal, Dubey, & Singh, 1985; Reen, Jamwal & Taneja, 1993) and of glucuronidation (Singh, Dubey, & Ata, 1986). A molecular mechanism is proposed for killing of breast cancer stem cells involving inhibition of Wnt signaling (Kakral, Brenner, Khakaya et al.,

2010). Evidence revealed increased generation of ROS in piperine-treated cancer cells (Yaffe, Doucette, Walsh, & Hoskin, 2013; Moorthy & Kathiresan, 2013). The AO N-acetylcysteine decreased apoptosis in the treated cells, demonstrating that the induced cytotoxicity was mediated by ROS, at least in part.

The unifying mechanism of ET-ROS-OS can also be applied by two methods. In one case, the polyene benzenoid structure in conjugation with amide may participate in ET. In the other instance, the catechol ether portion undergoes oxidative dealkylation to form a substituted catechol with subsequent oxidation to ET o-quinone.

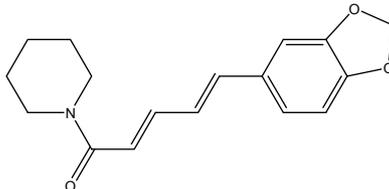


Figure 9. Piperine

11. Polyene-Lycopene

Lycopene (Figure 10), possessing a red color, is found in tomatoes, watermelon and pink grapefruit (Scarpa & Ninfali, 2015). Research demonstrates that vegetables with high amounts of the polyene decrease various cancers, such as prostate, cervic and digestive systems (Dow, 2005). A mixture of the compound with selenium and vitamin E inhibits prostate cancers with increase in survival. Growth of lung cancer cells is suppressed. Lycopene from tomatoes may act against prostate cancer, although the evidence is not conclusive (Choi & Lee, 2015). Also, mitochondrial dysfunction occurred. A similar report deals with action as a bactericide involving the hydroxyl radical which damages E.coli DNA. Cell filamentation also took place (W. Lee & D. G. Lee, 2014).

There are numerous reports of AO action displayed by lycopene with several examples provided herein. A study indicated possible alleviation of OS (Chen, Song, & Zhang, 2013). Administration of the polyene provided protection from mitochondrial dysfunction and OS (Snadhir, Mehrotra, & Kamboj, 2010). The compound is a powerful radical scavenger and its AO properties are involved in many health effects (Kujawska, Ewertowska, Adamska et al., 2014). A tomato paste suppressed OS in rats. Lycopene pretreatment suppressed ROS generation and increased survival (Kim, Han, Lee et al., 2015).

A 2006 book provides rationale for the ability of certain compounds to act as both pro- and anti- oxidants (Kovacic & Somanathan, 2006).

Relevant information concerning mechanism in relation to amphotericin B is presented in the section on β -carotene.

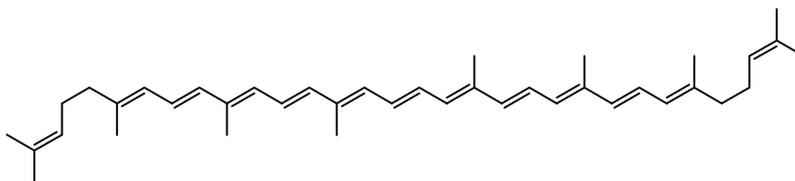


Figure 10. Lycopene

12. Polyene- β -Carotene

β -Carotene (Figure 11) (Scarpa & Ninfali, 2015). An orange-red pigment, occurs in carrots, pumpkins and sweet potatoes. The polyene reduces the risk of breast cancer in women before menopause. β -Carotene was found to exacerbate UV carcinogenesis in mice (Black & Gerguis, 2003). A mode of action was suggested for the repair of the β -carotene radical cation, a potent oxidizing entity formed by reaction with oxidizing species.

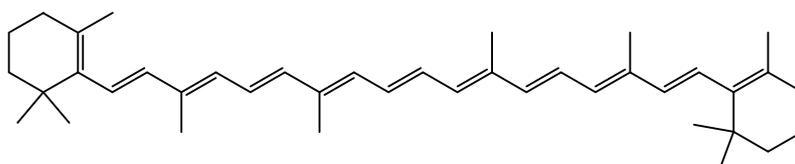


Figure 11. B-Carotene

Useful information is provided by electron affinity (EA) studies on amphotericin B (Figure 12) (Kovacic & Cooksy, 2012). The EAs are found to be 1.30 and 1.36 eV for the conformers. These values are considerably higher than those prominent ET functionalities, such as quinones (0.54-0.64 eV) and aromatic nitro compounds (0.59 eV for dinitrophenol). The EA values should be more favorable for lycopene having eleven conjugates and β -carotene with nine versus seven for amphotericin B.

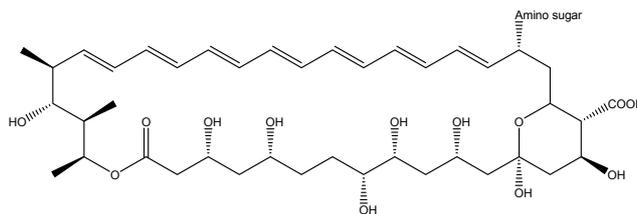


Figure 12. Amphotericin B

13. Conclusion

Nutrients display various beneficial and harmful effects with focus on anticancer action. The ET-ROS-OS scheme serves as unifying mechanism. Polyenes and ET quinone metabolites appear to play roles as ET agents. Evidence indicates involvement of nutrients as AOs in some actions. The unifying mode of action adds to prior studies.

Acknowledgements

Editorial support by Thelma Chavez is acknowledged, as well as topic suggestion by Darlene Nowack and literature search by Linda Muroi.

Competing Interests Statement

The authors declare that they have no competing or potential conflicts of interest regarding the publication of this paper.

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