REVIEW

Interactions between Reactive Oxygen Species and Cancer: the Roles of Natural Dietary Antioxidants and their Molecular Mechanisms of Action

Ademola A Oyagbemi*, OI Azeez, AB Saba

Abstract

Reactive oxygen species (ROS) are natural products inevitably generated along with cellular metabolism. Due to their extreme reactivity, they can damage DNA, proteins and lipids. Dietary antioxidants have been shown to take part in cellular reduction-oxidation (redox) reactions in which they can act as either antioxidants (election donors) or pro-oxidants (election acceptors) depending on the physiological environment and general oxidative state. Organisms have developed efficient machinery and mechanisms to keep the production of ROS under tight control, these same mechanisms have also been found to regulate other intracellular processes. p53 is a sequence-specific transcription factor and critical tumour suppressor gene that is most frequently mutated in human cancer. Cancer, one of the leading causes of death worldwide, can now be ameliorated, blocked or reversed with ubiquitous polyphenolic and organosulphur compounds present in natural dietary antioxidants.

Key words: Reactive oxygen species - DNA damage - cancer - antioxidant phytochemicals

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Introduction

Reactive oxygen species (ROS) are natural products inevitably generated along cellular metabolism (Lien et al., 2008). Due to their extreme reactivity, they can damage DNA, proteins and lipids. High levels of ROS have been shown to induce apoptosis as chronic high levels can promote vascular diseases such as arteriosclerosis (Lien et al., 2008). ROS include superoxide anion (0_2-), hydrogen peroxide (H_2O_2) and highly reactive by-product of H_2O_2 with hydroxyl radicals (OH) that are capable of reacting with and damaging DNA, proteins and lipids (Rajesshwar,1996).

Under normal conditions, cells utilize antioxidant defense systems to balance these toxic products (ROS) to keep the cells in a state of redox homeostasis (Lien et al., 2008). The deleterious effects of oxygen are said to result from its metabolic reduction to these highly reactive and toxic species (Buechter, 1988). Oxidative damage to cellular DNA has been reported to lead to mutation (Gulam & Haseeb, 2006) and this plays an important role in the initiation and progression of multistage carcinogenesis. Alterations in DNA such as base modification, rearrangement and miscoding of DNA base sequence, miscoding of DNA base sequence, gene duplication and subsequent activation of oncogenes are all known to be involved in initiating various cancers. Reactive oxygen species (ROS) and the related oxidative damage have also been implicated in the pathogenesis of various chronic human diseases (Pincemail, 1997; Ames, 1993; Witztum, 1994; Halliwell, 1993).

ROS can cause tissue damage by reacting with lipids in cellular membranes, nucleotides in DNA (Ahsan et al., 2003) and sulphydryl groups in proteins (Knight, 1995). Halliwell (1997) reported that free forms of ions are generated in the decomposition of ion-containing natural sources such as hemoglobin and ferritin. ROS can also be formed through lipid oxidation and photo-sensitizers when exposed to light (Boff and Min, 2002). Pro-oxidative enzymes such as lipo-oxygenase can generate free radicals (Spiteller, 2001) and significant amount of ROS can be generated through cross-linking/fragmentation of ribonucleoproteins (Waris & Alam, 1998). The relatively un-reactive superoxide anion radicals is converted by superoxide dismutase (SOD) into H_2O_2 which in turn take part in the "Fenton reaction" with transition metal ion (copper or iron) as catalysts to produce the very reactive hydroxyl radical (Aruoma, 1989; Halliwell & Gutteridge, 1990; 1992). Oxygen derived from free radicals have also been implicated directly or indirectly in a wide arrays of clinical disorders such as atherosclerosis, reperfusion injury, pulmonary toxicity, macular degeneration, cataracto-genesis, and cancer (Knight, 1995).

Dietary antioxidant has been shown to take part in cellular reduction-oxidation (redox) reactions in which they can act as either antioxidants (election donors) or prooxidants (election acceptors) depending on the physiological environment and general oxidative state

*Department of Veterinary Physiology, Biochemistry and Pharmacology, Faculty of Veterinary Medicine, University of Ibadan, Oyo State, Nigeria *For correspondence: ademolaoyagbemi@yahoo.com, aa.oyagbemi@mail.ui.edu.ng*

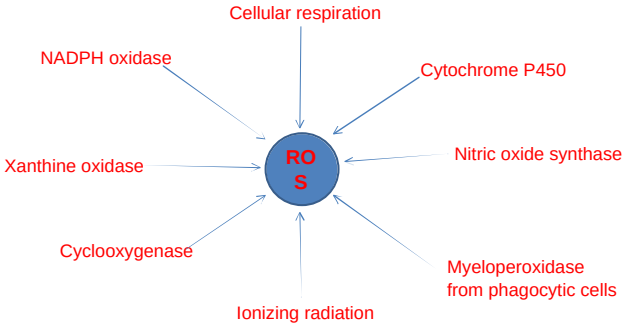

Figure 1. Sources of Reactive oxygen Species

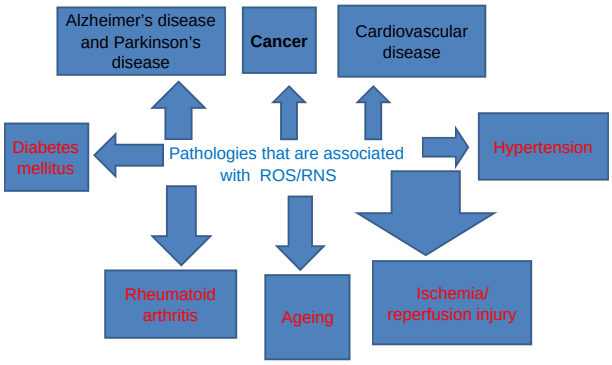

Figure 2. Diseases Associated with ROS and RNS

(Schwart, 1992; Palozza, 2002). Flavonoids which act as antioxidants include epigallocatechin gallate (tea), quercetin e.g. from onion, red wine, and berries, genistein (soybean), and taxifolin from citrus fruits (Heim, 2002). Other classes of dietary phytochemicals have been shown to considerably attenuate ROS generation that can take part in redox reactions in addition to flavonoids include broad categories of carotenoids (IARC, 1998) and organosulfur compounds (Bianchini and Vainio, 2001).

Generation of ROS

ROS are formed via several mechanisms (see Figure 1) including (1) ionizing radiation on biological molecules, (2) as an unavoidable by-product during cellular respiration, and (3) synthesized by enzymes (NADPH oxidase and myeloperoxidase, from phagocytic cells to battle against bacterial infection (Martindale and Holbrook, 2002; Klaunig & Kamendulius, 2004; Poli et al.,2004). Fibronectin, a major component of extracellular matrix, has been reported to stimulate ROS production through activation of NADPH oxidase dependent and NADPH oxidase independent pathways and 5'lipoxygenase mediates these pathways (Mouad et al. 2005).

Under the conditions of normal metabolism the most important source of superoxide anion (O_2-) is the mitochondrial electron transport chain, which leaks a few electrons directly onto O_2 as part of normal metabolism. It is estimated that 1 % to 3% of O_2 reduced in mitochondria is in the form of O_2- Turrens (2003). This product comes from two sites, complex 1 (NADH dehydrogenase) and also complex III (ubiquinone-cytochrome c reductase), with the latter being the major source under normal conditions (Salvemini and Cuzzocrea, 2002).

Several enzymes also contribute to O_2- production. One of the best characterized is xanthine oxidase (XO), which is present in the cytosol of many tissues and circulating blood or bound to glycosaminoglyan sites in the arterial wall (White, 1996). Normally, the enzyme acts as a dehydrogenase and transfers electrons to NAD^+ rather than O_2, in ischemia reperfusion (Ullrich and Bachschmid, 2000; Mueller, 2005) or in sepsis (Mueller, 2005; Brandes et al., 1999) in which the active site of the enzyme is oxidized and the enzyme acts as an oxidase and produces O_2-. The same is the case with a number of metabolically active enzymes as part of their normal function or when there is inadequate substrate. For example, cytochrome P450 enzymes in its reaction cycle can produce O_2- as a side reaction when they breakdown target molecules (Halliwell and Gutteridge, 1999).

Nitric oxide synthases, the family of enzymes that produce NO·, produce O_2- when the substrates L-arginine or co-factor tetrahydropteridines are insufficient (Mueller, 2005; Xia, 1996; and Xia, 1997)]. O_2- can also be produced by cyclooxygenase as part of arachidonic acid metabolism. O_2- even can be produced through auto-oxidation of molecules such as gylceraldehyde, $FMNH_2$, $FADH_2$, adrenalin, noradrenalin, dopamine and thiol containing molecules such as cysteine in the presence of O_2 (Salvemini and Cuzzocrea , 2002; Halliwell and Gutteridge, 1999). A number of diseases are associated with ROS or reactive nitrogen species (see Figure 2).

DNA damage and cancer

DNA damage by ROS has been accepted as a major cause of cancer according to Ames (1993). Increase coupled with deficient repair systems has been found to contribute significantly as major risk factors in diseases such as chronic hepatitis, cystic fibrosis, and various autoimmune diseases associated with increased risk of cancer (Hagen et al., 1994; Shimoda et al., 1994; Brown, 1995; Waris, 2005). ROS have been reported to be involved in modification of guanine, causing G-T transversions (Lunec, 2002). When critical genes such as oncogenes or tumour suppressor genes are affected, initiation/ progression can result (Ames 1994; Moller, 1994). In human tumour, DNA base modifications including G to T transversions have been shown to be the most frequent mutations in the P53 suppressor gene (Harris and Hollstein, 1993). Elevated levels of modified bases in cancerous tissue have been reported to result from production of large amount of H_20_2 which is characteristic of human tumour cells (Szatrowski & Nathan, 1991; Olinski, 1998). Activated carcinogens are known to exert their biological effects by forming covalent adducts with the individual nucleic acids of DNA or RNA. Similarly, reactive oxygen species (ROS), such as superoxide anions, hydrogen peroxide, and hydroxyl radicals, have been found to attack both DNA bases and the deoxyribosyl backbone of DNA (Bianchini et al., 2001).

DNA adducts particularly distort the shape of the DNA molecule, potentially causing mistranslation of the DNA sequence. Secondly, when the DNA replicates, an adducted base that persists unrepaired can be misread, producing mutations in critical genes, such as oncogenes and tumour suppressor genes. Thirdly, repair of bulky adducts can

result in breakages of the DNA strand, which can, in turn, result in mutations or deletions of genetic material (Knight, 1995). Numerous DNA repair pathways are known to exist and function to prevent the persistence of damage in DNA and are integral to the maintenance of genome stability and prevention of cancer (Martindale & Holbrook, 2002). Various DNA repair mechanisms include direct repair, base excision repair, nucleotide excision repair, double-strand break repair, and repair of inter-strand cross-links (Klaunig & Kamendulius, 2004).

DNA damage and p53

p53 is a sequence-specific transcription factor and critical tumour suppressor gene most frequently mutated in human cancer (Levine, 1997). p53 trans-activates genes that mediate apoptosis and has roles in DNA repair, senescence, and cell cycle arrest. There is enough compelling evidence that the primary physiologic role of p53 in DNA damage–induced apoptosis is to function as a transcriptional activator of genes encoding apoptosis effectors. p53 directly activates transcription of several genes encoding members of the Bcl-2 family, but it also mediates cell death through a variety of other mechanisms, including down-regulation of anti-apoptotic genes such as Map4 and survivin and up-regulation of pro-apoptotic genes such as Bax, IGF-BP3, DR5, Fas, and Apaf-1, as well as various other apoptosome components representing potential key therapeutic targets (Woods & Vousden, 2001; Hajra and Liu, 2004; Slee, 2004). p53 has also been shown to exhibit a direct apoptogenic role in the mitochondria, where it translocates and interacts with Bcl-xL and Bcl-2 proteins to induce mitochondrial permeabilization (Mihara, 2003) . Moreover, p53 deficiency leads to inappropriate survival of cells with DNA damage and therefore predisposes individual to develop neoplasia.

Recently, p63 and p73 proteins have also been identified that bind p53 response elements and trans-activate p53-associated genes and, as a result, induce apoptosis. Furthermore, there is extrinsic overlap of p53 and multiple transcriptional targets, in which p53 can activate at least two proteins in the intrinsic pathway, including Bax and p53-apoptosis inducing factor (Harms, 2004). Reactive oxygen species have been strongly correlated with p53-mediated apoptosis. Upon over-expression of p53, ROS levels rise, and mitochondrial apoptosis is induced as aforementioned. Inhibition of ROS-mediated apoptosis has also been reported in smooth muscle cells (Johnson, 1996).

ROS and Cell signalling

ROS are potentially highly toxic molecules released during redox reactions and they are part of the basic chemical processes of life (Finkel, 1998; Finkel & Holbrook, 2000) (see Figure 3). Organisms have developed efficient machinery and mechanisms to keep the production of ROS under tight control, these also regulating other intracellular processes (Forman et al. 2002; Droge, 2002; Thannickal & Fanburg, 2000; Schafer & Buettner, 2001; Janssen-Heininger, 2000) or can activate

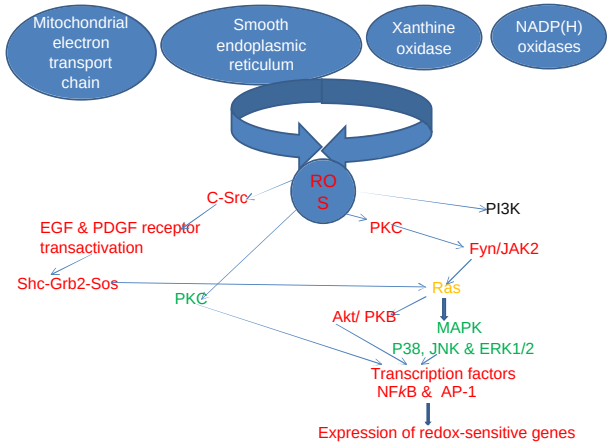

Figure 3. ROS-Mediated Mechanisms

diverse signaling pathways and affect arrays of various gene expressions. Lien et al., (2008) recently reported activation of Mitogen-activated protein kinases (MAPKs), phospholipase C-Y(PLC-γ) signaling, Protein Kinase C (PKC), p53 signaling, ataxia-telangiectasia-mutated (ATM) kinase, nuclear factor kappa B (NF-κB) and Jak/ Stat pathway by ROS. The MAPK signaling pathways modulate gene expression, mitosis, motility, metabolism, and programmed cell death (Gulam and Haseeb, 2006).

A lot of evidence indicating that ROS and the redox state have a signaling role in bacteria and plants has been reported, but there was scanty evidence in mammalian cells until recently. For example, in bacteria, the transcription factor OxyR is redox sensitive. There is now an increasing number of examples of ROS-based signaling in animals, including protein tyrosine phosphatase 1B (PTP-1B) (Lee, 2002), thioredoxin (Saitoh et al., 1998), SERCA2 (Adachi et al., 2004) and Ras (Adachi et al., 2004). Nitric oxide (NO·) is a well-characterized radical that has a major role in normal physiological functions. This radical has a central role in the regulation of vascular tone, nerve function and immune regulation. Even the potentially toxic by-products of NO· and O_2-, OONO·, has been shown to contribute to control of vascular tone (Adachi et al., 2004).

Cohen and coworkers found that NO· induced dilatation occurs by the production of low concentrations of OONO·, which directly stimulates the sarco/ endoplasmic reticulum calcium (Ca^{2+}) ATPase (SERCA) to decrease intracellular Ca^{2+} and thereby produce vasodilatation. This occurs by reversible S-glutathiolation of the thiol of a cysteine molecule on SERCA. Thus, by removing O_2- and preventing the formation of OONO·, superoxide scavengers actually blocked NO-induced vascular relaxation. However, high levels of oxidative stress, including high concentrations of OONO·, have been reported to result in irreversible oxidation of key thiols and prevented normal NO· induced relaxation. Endothelial and neuronal cells that use NO for signalling produce NO in small amounts, whereas macrophages and neutrophils that use NO to attack invading organisms produce it in large amounts. In the same vein, the NAD(P)H oxidase in phagocytic cells produces large quantities of O_2-, whereas the NAD(P)H oxidases in non-phagocytic cells produce much smaller amounts, consistent with a signalling role.

The MAPK kinase signaling cascades include

extracellular signal-related protein kinases (ERKs), JNKs/ stress-activated protein kinases (SAPKs), and p38 kinases. The ERKs transmit signals initiated by growth promoters, including EGF, PDGF, and fibroblast growth factor (FGF) and may ultimately foster cell growth and survival (Bode and Dong, 2004). The polyphenols; curcumin, EGCG, and resveratrol downregulate phosphorylation and ligand binding of growth factor receptors including EGF, FGF, and PDGF (Manson, 2005). Consequently, this quenches MAPK signaling, transcription factor activation (i.e., AP-1), and ultimately gene expression. It is noteworthy that many cells require such signals to avoid apoptosis, and, as a result, interruption of this signaling encourages induction of apoptosis in many cell types. For example, the indirect inhibition of PI3-Akt anti-apoptotic signals might contribute to cell death through modulation by diet (Chen and King, 2005). The MAPKs are activated by translocation to the nucleus, where they phosphorylate numerous substrates, including the transcription factors AP-1 and NF-κB. Activation of both are linked to carcinogenesis and promotion (Bode and Dong, 2004).

Indeed, numerous mutations can occur in tumour suppressor genes involved in induction of apoptosis, and these include p53, p19, ARF, Rb, PTEN, TRAIL, and CD95/Fas (Johnstone, 2002). Numerous oncogenes may also be activated through mutation to inhibit or circumvent the inherent controls of apoptosis, and critical oncogenes involved include Bcl-2, MDM2, IAPs, NF-κB, Akt, PI3K, Ras, Myc, and FLIP (Johnstone, 2002). Blocking the expression of these genes, and in particular oncogenic ras, is currently an active pharmacological approach for cancer therapy (Adjei, 2001). Mutations in genes that regulate apoptotic pathways are common in most cancers, emphasizing their importance for DNA damage (Sun et al., 2004).

Many dietary agents can affect cellular signaling. Resveratrol stimulates complex formation between p53, ERK, and p38 kinase, with enhanced phosphorylation, stabilization, and activation of p53 in epidermal cells (Roemer and Mahyar-Roemer, 2002). Indole-3-carbinol potently inhibits signaling through protein kinase B and binding of NF-κB to DNA (Howells et al., 2002). Indole-3-carbinol and DIM also inhibit the MAPK pathway, which may inhibit cancer cell survival. Curcumin reduces the activity of p38 MAPK, and EGCG inhibits tyrosine kinase and MAPK activation in transformed cells but not in normal cells. Capsaicin, a principal pungent ingredient of hot red and chili peppers, markedly activates JNK-1 and p38 MAPK signaling in Ha-ras–transformed human breast epithelial cells (Hail, 2003). In cells with mutated oncogenic Ha-ras, green and black tea polyphenols potently inhibited ERK phosphorylation and AP-1 activity (Chung et al. 1999). Allyl ITC (AITC), BITC, and PEITC increased activity of JNK in HL-60 cells. MAPK, ERK, and p38 kinase were activated by PEITC in HT29 and PC3 cells. Similarly, BITC has been shown to activate p38 kinase in human head and neck squamous cell carcinoma lines (Zhang, 2004). In the same vein, garlic compounds, DADS potentially induced ROS and JNK, S-allylmercaptocysteine induced JNK-1 activation and jun kinase activity, as well as ajoene activated MAPKs (JNK, p38, ERK1/2) in different cell types (Wu et al., 2005).

The role of ROS in the signaling of a number of growth factors has also been well established. A superb example is the role of ROS in angiotensin signaling as established by Griendling and co-workers (Griendling et al., 2000; Griendling et al. 1994; Ushio-Fukai et al., 1999 and Zafari et al., 1998).This group of researchers showed that exposure of vascular smooth muscle to angiotensin II results in smooth muscle growth that is dependent upon increased production of O_2- by NAD(P)H oxidase and its subsequent dismutation to H_2O_2. H_2O_2 then activates downstream prosurvival pathways with resultant vascular hypertrophy. Other growth factors such as platelet derived growth factor (PDGF) have been shown to have similar signaling mechanisms (Sundaresan et al., 1995) ROS also play a significant role in the intracellular signaling of tumour necrosis factor-α (TNF-α) (Matsubara & Ziff, 1986; Ferro et al., 1997; Ferro et al., 19998; De Keulenaer et al., 19998; Murphy et al., 1992; Phelps et al., 1995; Goode & Webster, 1993; Lum & Roebuck, 2001 & Demling et al., 1986) and this probably occurs through O2- produced by NAD(P)H oxidase and regulation of the transcriptional activity of NFκB. Also, it has recently been shown that lipopolysaccharide activation of Toll-like receptor 4 increases O_2- production by NAD(P)H oxidase and this too leads to NFκB activation (Park et al., 2004).

Properties of some Chemopreventive Agents and their Molecular Mechanisms of Action

Resveratrol

There is mounting evidence in the literature that Resveratrol is a promising natural compound for prevention and treatment of a variety of human cancer (Fulda and Debatin, 2006). Resveratrol, trans-3, 5, 41-trihydroxy-trans-stilbene, is a phytoalexin produced by plants, and the skin of red grapes. Resveratrol affects all three stages of carcinogenesis, namely initiation, promotion and progression (Mohammad, 2007). Resveratrol has been shown to block carcinogen activation and subsequent DNA damage by suppressing induction of Phase I metabolizing enzymes (Kudu and Surh, 2005).

The anticarcinogenic effect of resveratrol has been found to be closely associated with its antioxidant activity, through which it inhibits cyclooxygenase, hydroperoxidase, protein kinase C, Bcl-2 phosphorylation, Akt/protein kinase B, focal adhesion kinase, NF-KB, matrix metalloproteinase-9, and cell cycle regulators. Exposure of normal cells to resveratrol results in the activation of a series of upstream kinases such as ERK, JNK and P13K, with dissociation of nuclear factor related erythroid factor 2 (NrF2) from its inhibitory counterpart keap1. Free NrF2 translocates to the nucleus, where it regulates transcriptional activation of genes encoding phase II detoxification/antioxidant enzymes (Kudu and Surh, 2005). Resveratrol has been reported to modulate diverse signal transduction pathways resulting in the blockade of carcinogen activation and enhancement of detoxification, inhibition of inflammation, cell proliferation, and apoptosis (Kudu and Surh, 2005). Antioxidant activity of resveratrol has been attributed to

its ability to inhibit H_20_2 production, myeloperoxidase activity and restoration of glutathione levels and activity of superoxide dismutase (Jang & Pezzuto, 1998). Resveratrol has also been reported to inhibit COX-2 at both transcriptional and post-transcriptional levels (Subbaramaiah et al., 1998). It also down regulates the expression of both COX-1 and COX-2 mRNA transcripts in NMBA-induced esophageal tumour in F34A rats (Li et al., 2002) and inhibition of LPS, TPA or H202-induced mobilization of arachidonic acid and expression of COX-2 which results in decrease PGE2 production (Martinez and Moreno, 2000). Resveratrol has been shown to inhibit the expression of various Cyclins (e.g. D1, D2 and E) as well as the expression and catalytic activities of Cyclins dependent kinases (CDK) -2, -4 and -6 suggesting that resveratrol-induced up regulation of p21WAF-1/CIP-1 may inhibit the formation of Cyclin-cdk complexes thereby imposing artificial check points at GI/S transition of the cell cycle (Ahmad et al., 2001) and induces stabilization and activation of p53 (Roemer and Mahyar-Roemer, 2002).

Lycopene

Lycopene is known to be an effective scavenger of reactive oxygen species, including singlet oxygen (O_2^1) and other excited species (Stahl et al., 1998 & Woodall et al., 1997). Lycopene is the strongest singlet oxygen quencher as well as potent antioxidant compared to other carotenoids. Lycopene is mainly contained in tomatoes and high concentration is found in processed tomato products like ketchup, tomato sauce/juice as well as in red coloured fruits like water melon and guava. Intake of lycopene has been inversely linked to the incidence of prostate cancer (Giovannucci et al., 2002; Sesso et al., 2004). Lycopene is the main carotenoid in tomatoes and tomato-products and is responsible for the red colouration of tomatoes (Hwang and Lee, 2006). Suggested inhibitory mechanisms for lycopene include enhancing gap junction intercellular communication (Krutvoskikh et al., 1997), cell cycle arrest (Hwang and Bowen, 2000), suppression of tumour cell proliferation and apoptosis (Kim et al., 2001). Lycopene is one of the most potent antioxidants (Miller et al., 1996) and has been suggested to prevent carcinogenesis and atheriogenesis by protecting critical macromolecules including lipids, low-density lipoproteins (LDL), proteins and DNA (Rao & Agarwal, 1998; Pool-Zobel, 1997). Lycopene, because of its high number of conjugated double bonds, exhibits higher singlet oxygen quenching ability compared to β-carotene or α-tocopherol (Dimasco et al., 1989). Lycopene in small doses reduced the N-methylnitrosourea (MNU) induced development of aberrant crypt foci (ACF) in the colon of Sprague-Dawley rats (Narisawa et al., 1998), dimethylbenzanthracene (DMBA)-induced mammary tumour (Sharoni et al., 1997) and diethylnitrosamine (DEN) induced liver pre-neoplastic foci in rats. Ingestion of tomato juice has been shown to inhibit the development of N-butyl-N-(4-hydroxybutyl) nitrosamine (BBN)-induced development of urinary bladder in transitional cell carcinomas in male Fischer 344 rats (Okajima et al., 1998), protection against azoxymethane (AOM)-induced colonic pre-neoplastic lesions (Jain et al., 1999). Similarly, lycopene has also been shown to protect against microcystin-induced mouse hepatocarcinoma by suppressing the phosphorylation of regulatory proteins such as retinoblastoma gene protein product and arresting cells in the Go/GI phase of cell cycle similar to P53 function (Matsushima et al., 1995)

Curcumin

Curcumin, a widely used spice and colouring agent in food, has been shown to possess potent antioxidant, antitumour promoting and anti inflammatory properties *in vivo* and *in vitro* (Motterlini et al., 2000). Copper complex of Curcumin was found to show promising superoxide dismutase (SOD) activity with comparable free radical scavenging ability and an improved antioxidant efficacy; meaning that Curcumin could also act as antioxidant enzyme. Curcumin was recently reported to protect against dimethyl nitrosamine (DMN)-induced hepatoxicity through antioxidant response element (ARE)-driven induction of heme-oxygenase-1 [HO-1] expression (Farombi et al., 2008). The increased haeme-oxygenase activity is an important component of Curcumin-mediated cyto-protection against oxidative stress. Pretreatment of human colonic epithelial cells with Curcumin has been shown to inhibit TNF-α-induced cycloxygenase -2 (COX-2) gene transcriptions and NF-κB activation and inhibition of IKB degradation by down regulation of NF-κB-inducing kinase (NIK) and IKB kinase (IKK). Curcumin was shown to inhibit 1KB phosphorylation in human multiple myeoloma cells (Bharti et al., 2003) and murine melamoma cells through suppression of IKK activity, and this taken together contributes significantly to its antiproliferative, pro-apoptotic and/or anti-metastatic activities.

Capsaicin

Hot red chili pepper which belongs to the plant genus capsicum is widely consumed all over the world. Nigeria is not an exception. 8,-methyl-N-Vanilly-6-nonenamide is the principal phenolic compound in capsaicin. Chemopreventive properties of capsaicin have been reported (Surh and Lee, 1995; Surh, 2002; Philip & Kundu, 2003). Topical application of capsaicin has been shown to inhibit PMA-induced mouse-skin tumour formation (Park et al., 1998) and activation of NF-κb (Han et al., 2002). The anti-proliferative property of capsaicin has been ascribed to its ability to induce apoptosis (Lee et al., 2000; Jung et al., 2001). Generation of reactive oxygen species (ROS) is one of the mechanisms by which capsaicin induce apoptosis in tumour cells. Macho et al (1998) reported induction of apoptosis in cultured Jurkat cells through generation of reactive oxygen species (ROS) and rapid activation of C-JUN NH_2-terminal kinase (JNK).

Capsaicin also causes G1 arrest of endothelial cell through down-regulation of cyclin D1 and vascular endothelia growth factor (VEGF) induced angiogenic signaling pathways. Cyclin D1 is required for the activity of cyclin-dependent kinase 4(CDK4) which phosphorylates RB (tumour suppressor gene), thereby releasing E2F to mediate the transition of G1 to S, which in turn leads to DNA synthesis and cell cycle progression (Jeong, 2004) and this pathway is blocked by capsaicin. It

has been documented that other anti-angiogenic molecules such as endostatin and Curcumin also suppress (Retinoblastoma gene) Rb phosphorylation and DNA synthesis of endothelial cells through down-regulation of cyclin D1 (Mukhopadhay et al., 2002; Hanai et al., 2002). In fact, capsaicin was reported to block the downstream event of Vascular endothelial growth factor (VEGF) induced KDR/FIK-1 signaling such as activation of p38 mitogen activated protein kinase and p125 FAK tyrosine phosphorylation that are required for the mitogenic activity of VEGF in endothelial cells (Bernatchez et al., 1999; Zachary & Gliki, 2001 & Davis-Smyth, 1996). Capsaicin modulates the activities of pro-inflammatory mediators and the intracellular signaling cascades. Researches are currently being carried out to unravel the molecular mechanisms of action and other signaling pathways that are associated with capsaicin anti tumour effects.

Sulphoraphane

Sulphoraphane (SF) is a naturally occurring isothiocyanate which has a potent anticarcinogenic capability in experimental animal models. This isothiocyanate is quantitatively resident in broccoli and has been shown to be a potent inducer of phase 2 detoxification enzymes e.g. glutathione S-transferases (GSTs), and also known to block metabolic activation of chemical carcinogens in experimental animal models (Zhang et al., 1992). Other mechanisms associated with antiproliferative and chemopreventive activity of sulphoraphane include induction of apoptosis, cell cycle arrest, anti-inflammation and ability to inhibit phase I enzymes that might be involved in activation of chemical carcinogens to ultimate carcinogens (Chung et al., 2000; Zhang, 2000). It was recently shown that SF, as well as some of its analogues, rapidly accumulated in all cell lines tested, and its intracellular concentrations can reach millimolar levels (Zhang and Talalay, 1998; Zhang, 2000). SF appeared to enter cells freely, but was almost entirely conjugated with GSH in cells (Zhang, 2000; 2001). Results from investigations revealed that cellular GSH was the principal driving force for accumulation while cellular GST further enhances such accumulation (Zhang and Talalay, 1998; Zhang, 2001).This mechanism is consistent with the fact that SF undergoes spontaneous conjugation with GSH under mild conditions to give rise to the corresponding dithiocarbamate (GS-SF) and that the reaction is accelerated by GST (Kolm et al., 1995). Preliminary evidence suggests that the accumulated GS-SF may be further metabolized, such as by binding to cellular proteins and the formation of other dithiocarbamate metabolites (Zhang, 2000; Kassahun et al., 1997). Cellular accumulation of SF appears critical for its anticarcinogenic activity, related to its induction of many Phase 2 detoxication enzymes in cultured cells (Zhang & Talalay, 1998; Ye & Zhang, 2002).

Caffeic acid phenethyl ester (CAPE)

Caffeic acid phenethyl ester (CAPE) is an active component of propolis from honeybee hives (honeybee resin). CAPE has been shown to have anti-inflammatory, anti-carcinogenic and immunomodulatory properties (Grunberger et al., 1988 ; Abdel-Latif et al., 2005). CAPE was shown to suppress acute inflammation (Orban et al., 2000), acts as specific inhibitor of NF-κB (Natarajan et al., 1996) and inhibition of nuclear factor of activated cells (NFAT) and activator protein-1 (AP-1) nuclear binding and activation. CAPE also alters the redox state, induces apoptosis, suppresses lipid peroxidation and acts as an antioxidant (Kimura et al., 1984; Chiao et al., 1995; Laranjinha et al., 1995) and inhibits COX-2 expression (Kim et al., 2001). The inhibitory potentials of CAPE on different transcription factors provide direction and deep insight into the nuclear mechanism(s) of actions underlying the chemopreventive properties of CAPE. It has anti-inflammatory, anti-viral, anti-mitogenic, anti-carcinogenic, and immunomodulatory effects (Ozyurt et al., 2004; Song et al., 2000). It has also been reported that CAPE exhibits antioxidant activity and inhibits lipoxygenase activities, protein tyrosine kinase, and NFκB activation (Natarajan et al., 1996; Song et al., 2002). The possibility that CAPE displays pharmacological activity by inhibiting the release of arachidonic acid and the enzyme activities of cycloxygenase (COX)-I and COX-II have also been extensively discussed (Song et al., 2002).

Diallyl Sulphide (DAS)

Medicinal use of garlic has been dated back to antiquity. Diallyl sulphide is the fat soluble bioactive compound in garlic. DAS is an antioxidant and anti-inflammatory agent (Kalayarasan et al., 2008). DAS has been shown to reduce bleomycin-induced activation of inducible nitric oxide synthase (iNOS) and NFκB and decrease the augmented levels of the early inflammatory cytokines, tumour necrosis factor alpha (TNF-α) and interleukin I beta (IL-Iβ) in lung tissues (Kalayarasan et al., 2008). Thejass and Kuttan (2007) recently suggested that antiangiogenic activity of DAS can be related to its negative regulation of pro-angiogenic factors such as VEGF and proinflammatory cytokines and positive regulation of antiangiogenic factors such as IL-2 and TIMP. Apoptotic activity of DAS can be adduced from the work of Sriram (2008) which include increased production of ROS, cell cycle arrest, decreased cell proliferation and induction of apoptosis. DAS also promotes the expression of caspase-3 and suppresses the activity of extracellular regulatory kinase-2 (ERK-2). Other antioxidant and anticancer activities of DAS have also been reported by various authors (Green et al., 2007a; Green et al., 2007b; Arora et al., 2006; Thomas et al., 2004).

Conclusions

The use of chemopreventive agents in natural products has become the mainstay and novel sources of alternative therapy in our contemporary days. Their chemopreventive potentials which include antioxidant, antiproliferative, anticancer, antiangiogenic properties are now being utilized for human benefit to alleviate various forms of degenerative diseases including cancer. Cancer, one of the leading causes of death worldwide can now be ameliorated, blocked or reversed with these polyphenolic and organosulphur compounds present in these phytochemicals.

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