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# Chemopreventive compounds from plant derived food and their bioactivity

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## ABSTRACT

Terrestrial plants, especially higher plants, have a long history of use for the treatment of many human diseases such as ailment, cancer, diabetes, neurodegenerative and cardiovascular disorders. Since then, many studies have been designed to evaluate biochemical properties of whole plant extract, fractions or isolated compounds. Several researches have established the relation between consumption of plant derived products to minimize the oxidative stress and diseases associated with stress. These beneficial biological properties on animal health has been attributed to certain classes of metabolites contents in plants including anthocyanins, flavonols, tannins, carotenoids, terpenoids, alkaloids and vitamins. The bioactivity of these compounds is due to their ability to scavenge reactive oxygen species (ROS) or NOS or to modulate antioxidant enzymes expression. The devastating environmental pollution has burdened with numerous toxic chemicals of which biological compounds such as nucleic acid, proteins and membrane phospholipids were the potential targets leading to mutation, cell injury and death. The endogenous antioxidant systems falls prey in response to these toxic and deleterious oxidants and reactive oxygen species. In these conditions, exogenous chemopreventive compounds extracted from plant derived foods are required to maintain cell hemostasis. This review highlights the source and the chemopreventive mechanisms of genoprotective compounds from plant derived food.

**Key words:** Bioactivity; Chemoprevention; Genoprotection; Oxidative stress; Terrestrial plants

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## INTRODUCTION

Free radicals and their precursors are members of a reactive chemical family named reactive oxygen species such as·OH, O2$^{-\cdot}$, $H_2O_2$,$^1O_2$, ONOO. These reactive oxygen species are produced in normal cell metabolism.[1] Human beings exploits the use of beneficial compounds derived from plant products as defense mechanisms or as signal inside or inter cells. So a useful level of beneficial reactive species is maintained inside cell by an equilibrium between the generating system producing free radicals such as mitochondrial respiration, phagocytosis, redox cycle or radiations, and the antioxidant systems such as scavenger molecules absorbed from the diet (vitamin C, E, carotenoids, polyphenols) or produced endogenously (glutathione, thioredoxin) or such as antioxidant enzymes (superoxide dismutases, glutathione peroxidases).[2]When the production of pro-oxidant and their elimination by antioxidant systems were unbalanced, oxidative stress may unfortunately occur.[3] Oxidative stress damages intracellular macromolecules, oxidizing lipids, DNA or proteins.[1] Many cellular dysfunctions result from these biochemical damages, variable according to the level of stress: excess in cell proliferation, cell death by apoptosis, lipid deposition, and mutagenesis.[4]By creating such disorders, oxidative stress is partly responsible for aging and age-related diseases as cancer, cardiovascular disorders, and neurodegenerative diseases as Alzheimer disease.[1] DNA, one of the biological macromolecule is continuously degraded by endogenous oxidative stress leading to multiple types of DNA oxidative damages such as base oxidation, single or double strand breakage, mutation, DNA-protein cross links.[5]

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To combat these biological macromolecules damage, cell has developed a number of antioxidant system to thwart the deleterious attacks of oxidative stress species. So, many antioxidant enzymes in cell living such as catalase, superoxide dismutase and glutathione peroxidases have the main function to regulate the production and the elimination of oxygen oxidative species and constitute the first line of cell antioxidant defense.[6]

In certain situations, endogenous antioxidant systems fails to nullify the toxic radicals and the exogenous antioxidant compounds are destined to take over the endogenous antioxidant system. Many therapeutical strategies have been tested in animal and human to prevent the occurrence of these oxidative diseases.[6] They use nutritional improvement of antioxidant capacities, plant or chemical antioxidants.[7] Chemists designed various new molecules chelating iron, scavenging free radicals or catalyzing destruction by miming the activity of antioxidant enzymes. But new ways of research have to be now explored to create more specific and gene targeted molecules able to protect/repair DNA damages but not only to destroy oxygen radicals. This review highlights the source and the chemopreventive mechanisms of genoprotective compounds from plant derived food.

## BIOACTIVE COMPONENTS OF PLANT FOOD AND THEIR BIOACTIVITY

### Vitamins

Ascorbic acid commonly found in oranges, Citrus, Tomatoes, is essential for cell living. The possible use of ascorbic acid in cancer therapy and prevention has been an area of great interest. Thus it is tempting to speculate that ascorbic acid supplements, if able to prevent the formation and/or promote the repair of pre-mutagenic oxidative DNA lesions, could be of use in cancer prevention.[8] In addition, an early report showed that daily supplementation with ascorbic acid at high doses (grams) increased the survival time of terminal cancer patients and it was suggested that ascorbic acid could have important anticancer properties.[9] Indeed, ascorbic acid kills or inhibits the growth of many tumor cell lines. There are also several reports showing that cancer cell lines are more sensitive to ascorbic acid than their non-malignant counterparts.[10] It inhibits genotoxicity of dimethyl sulphate, ethyl methane sulfonate, methyl methane sulfonate and N-nitroso N-ethylurea in drosophila Ames test and repairs DNA damage induced by methyl methane sulfonate, cyclophosphamide, $FeSO_4$ and $CuSO_4$ in mouse blood cells in vivo.[11,12] Ascorbic acid has exhibited antimutagenic effect on norfloxacin and diethylnitrosamine-induced mutagenicity in Salmonella typhimurium strains TA97, TA98 and TA100.[4] It protected human skin from UV-irradiation and prevented DNA mutation by ROS scavenging.[13]

Vitamin E found in nuts, seeds and vegetable oils has glutathione regenerating properties and protect cell against oxidative stress injury. It inhibited norfloxacin and diethylnitrosamine induced mutagenicity in Salmonella typhimurium strains TA97, TA98 and TA100 and protected human skin from UV-irradiation.[4,13] Vitamin E has also exhibited genoprotective effect on diazinon-induced DNA damage in rat *in vivo*.[14]

### Carotenoids

Carotenoids such as β-carotene, lycopene, lutein, zeaxanthin as well as other carotenoids are found to be effective as anti-proliferative, anti-oxidant, learning and memory enhancer, sperm cryoconservation, biosurfactant as well as effective in brain neurodegenerative and Alzheimer disorders.[15] Beta-carotene is a strongly colored red-orange pigment abundant in vegetables and fruits, especially in carrots and colorful vegetables. Beta-carotene is only synthesized in plants, not in humans or animals. In plants, beta-carotene absorbs light and energy is transferred to the chlorophyll for photosynthesis. Through consumption of fruits and vegetables rich in beta-carotene, one can lower the chances of cancer and heart disease. Also, study suggests that beta-carotene is helpful in people with the genetic condition erithropoietic protoporphyria.[16] Intake of beta-carotene improves osteoarthritis, Alzheimer's disease, and cystic fibrosis. Additionally, beta-carotene helps protect the soft tissue and linings of the digestive tract, kidneys and bladder, and helps heal stomach ulcers.[16] Beta-carotene also protects the skin from aging, helps with the secretion of gastric juices necessary for proper digestion of proteins, helps building up strong teeth and bones and helps in the formation of visual purple, a substance that is in the eye necessary for proper night vision.[16] Additionally, beta-carotene enhances wound healing, soothes mucus membranes, eases aching joints, eases pain of arthritis and protects against colon cancer.[17] It protects human skin from UV-Irradiation and detoxifies hydrogen peroxide and L-arginine-induced DNA oxidative damage in human hepatocellular HepG2 Cells.[13,16] Lycopene found in tomatoes, papaya, oranges protected lungs against squamous metaplasia and human skin from UV-Irradiation as well as from γ-radiation.[13,18] It inhibits lipid peroxidation and possess antioxidant properties in primary culture of isolated rat hepatocytes *in vitro*. Additionally lycopene decreases the genotoxicity of N-methyl-N'-nitro-N-nitrosoguanidine.[19] The xanthophyllic carotenoids such as lutein and zeaxanthin present in spinach, kale squash, peas, cabbage and mays orange have antioxidant properties and protects skin from lipid peroxidation induced by skin UV irradiation.[20] Crocetin, the main bioactive compound of

saffron scavenge free radicals, especially superoxide anions protects cells from oxidative stress. Crocetin is useful as sperm cryoconservation and in protecting hepatocytes from toxins.[21] Because of its powerful antioxidant activity, it could be useful in the therapeutic intervention of neurodegenerative disorders. Recent developments on crocetin reveals that it do acts as a potent hepatoprotective agent, because of its protective property *in vivo* intoxication models in rats treated with aflatoxin B1 and dimethyl nitrosamine.[21] The effect might be due to the hepatic tissues defense mechanism, which elevates the cytosol glutathione and the activities of glutathione S- transferase and glutathione peroxidase.Crocetin regulates cell cycle arrest by inhibiting DNA synthesis and RNA polymerase II activity in cancer cell.[22]

### Terpenoids, omega-3 fatty acid and linoleic acid

Terpenoids, also referred to as terpenes, are the largest group of natural compounds frequently found in citrus fruits, cherries and grapes.[23]Most terpenes have biological activities and are used for the treatment of human diseases.[23,24]Terpenoids are commonly classified as monoterpenes ($C_{10}$), sesquiterpenes ($C_{15}$), diterpenes ($C_{20}$), triterpenes ($C_{30}$). These terpenes display a wide range of biological activities against cancer, malaria, inflammation and a variety of infection diseases (viral and bacterial).[25,26] The monoterpene d-limonene is an antitumor compounds by inducing apoptosis follow caspase-dependent mitochondrial death pathway in human leukemia cells.[27] Its homologue geraniol mediated cell cycle arrest by p21Cip1 and p27Kip1 in human pancreatic adenocarcinoma cells and inhibited DNA topoisomerases.[28]Studies reveals Menthol has anticancer activity by modulating the action of DNA topoisomerase I, II and promotes NF-I B expression in human gastric cancer SNU-5 cells.[29]Dehydrocrotonin, a major diterperne in *Croton cajucata* inhibits methyl methane sulfonate, doxorubicin and mitomycin-induced micronuclei and apoptosis in CHO-K1 cell.[30]Lupeol, a diterpene present in olive, mangoes, fig has modulating activity on NF-jB and PI3K/Akt pathways and inhibits skin cancer in CD-1 mice.[31]Ursolic acid, a triterpene compound have shown to possess genoprotective effect on *tert*-butyl hydroperoxide (*t*-BHP)-induced DNA damage in a human hepatoma cell line (HepG2).[32] Castasterone contained in algae inhibited $H_2O_2$-induced DNA damage in human lymphocytes.[33]Omega 3-fatty acid commonly found in algae and fish oils enhances NK cell-induced apoptosis of pancreatic cancer cells by linoleic acid down-regulation, phorbol ester-induced NF-kB activation and subsequent COX-2 expression in hairless mouse skin by targeting IkB kinase and PI3K-Akt.[34]

### Flavonoids and catechins

Flavonoids are a group of polyphenolic compounds; which are widely spread throughout the plant kingdom.[35]They are classified as flavones, flavanones, catechins and anthocyanins. Flavonoids possess pharmacological and biochemical effects, which inhibitsa number of enzymes such as aldose reductase, cyclooxygenase, xanthine oxidase, phosphodiesterase and lipoxygenase.[36] They also have a regulatory role on different hormones like androgens, estrogens and thyroid.[37] Recently, flavonoids were demonstrated to regulate signaling pathways by interaction with some regulator factors.[38] Flavonoids possess genoprotective properties and can be used to fight against cancer development.[35] Quercetin, Quercetin 3-O-α-L rhamnoside, Myrecitin and Myrecitin 3-O-α-L rhamnoside have exhibited anti-mutagenic activity in Salmonella strains TA98 (−S9,+S9) and TA97a (−S9).[39] Quercitrin, Isoquercitrin and Rutin, possess antioxidant properties and inhibits chromosome damage in human lymphocytes exposed to hydrogen peroxide.[40] Quercetin has also inhibited azoxymethane-induced colorectal carcinogenesis in F344 rats.[41]Rutin exhibits some genoprotective effect against tert butyl hydroperoxide-induced DNA damages in human HepG2 cell and protects mouse bone marrow cell against X-Ray–irradiation.[32,42]The tavonol kaempferol by its antioxidant properties protects human lymphocytes cells against the oxidative damages induced by hydrogen peroxide.[43] The flavone tangeritin induced cell-cycle G1 arrest through inhibiting cyclin-dependent kinases 2 and 4 activities and through elevating Cdk inhibitors p21 and p27 in human colorectal carcinoma cells.[44]. Acacetin suppresses LPS-induced up-expression of iNOS and COX-2 in murine macrophages and TPA-induced tumor promotion in mice.[45] Liteolin-7 glucoside has protective role against oxidation of DNA and stimulate DNA repair in cultured human cells.[46] Apigenin exhibited genoprotective effect against hydrogen peroxide-induced genotoxic damage on cultured human peripheral blood lymphocytes and inhibited pancreatic cancer cell proliferation through G2/M cell cycle arrest.[47,48] Its derivative 5 hydroxy 3,6,7,8,3',4' hexamethoxyflavone has anti-cancer properties and found to inhibit pancreatic cancer cell proliferation through G2/M cell cycle arrest, induced apoptosis through reactive oxygen species production, growth arrest and DNA damage-inducible gene 153 expression as well as caspase activation in human leukemia cells.[48,49]. It also exhibits inhibitory activity on 12-O-tetradecanoylphorbol 13-acetate-induced skin inflammation and tumor promotion in mice.[50] Common flavanol such as peracetyl epicatechin gallate, catechin, epigallate catechin gallatte, epicatechin and acid chlorogenic were genoprotective compounds. So, peracetyl epicatechin gallate has prevented skin carcinogenesis by suppressing the PKD1-dependent signaling pathway in CD34+ skin stem cells and skin tumors.[51] Catechin is an antioxidant and tumor cell growth modulators compound.[52]Epicatechin and chlorogenic acid enhanced the intrinsic cellular

tolerance against oxidative insults either by activating survival/proliferation pathways or by increasing antioxidant potential in HepG2 and so regulates cell apoptosis.[53] Epigallatecatechingallatte inhibited colorectal aberrant crypt foci (ACF) formation and prevented oncogenic changes in dysplastic ACF in azoxymethane-treated F344 rats.[54] The flavanone naringenin protected HaCaT human keratinocytes against UVB-induced apoptosis and enhanced the removal of cyclobutane pyrimidine dimers from the genome.[55] The isoflavonoid genistein induced apoptosis of human breast cancer MCF-7 cells involves calpain–caspase and apoptosis signaling kinase 1–p38 mitogen-activated protein kinase activation cascades.[56] Anthocyanins, major class of flavonoids has interesting biochemical activity due to their stability in food and their hydrogen donor ability. Delphinidin and cyanidin derived compounds such as delphinidin 3-glucoside, delphinidin 3 rutinoside, cyaniding, cyanidin 3-glucoside and cyanidin 3- rutinoside protected against DNA damage induced by *tert*-butyl-hydroperoxide in rat smooth muscle and hepatoma cells.[57]

### Proanthocyanidins and Flavanolignane

Proanthocyanidins are synonymous with condensed tannins and are found in fruits, berries, beans, nuts, cocoa and wine. The abundance of proanthocyanidins in plants makes them an important part of the human diet. Proanthocyanidins inhibited mitogenic and survival-signaling *in vitro* and tumor growth *in vivo*. Proanthocyanidins also inhibited carrageenan-induced paw edema in rats and suppressed LPS-induced inflammation.[6] Proanthocyanidin A2 treatment modulated antioxidant enzyme expression and decreased UVB-induced skin tumors.[6] Silibinin protected against photocarcinogenesis via modulation of cell cycle regulators, mitogen-activated protein kinases and Akt signaling.[58] Sylimarin protected human lymphocytes against L-arginine- induced genomic damages.[16] Dibenzylbutyrolactone lignin (-)-hinokinin has exhibited an inhibitory effect on doxorubicin and methyl methane sulfonate clastogenicity in V79 chinese hamster lung fibroblasts.[59] Secoisolariciresinol diglucoside protects non-malignant lung cells from radiation damage.[60] Lignin isolated from oil palm black liquor waste defends mouse bone marrow against cyclophosphamide genotoxicity.[61]

### Other phenolic compounds

Thymoquinone, the main essential oil of *Nigella sativa* L. seeds has exhibited a genoprotective activity on doxorubicin-induced damage in isolated human leukocytes.[62] It has also inhibited phorbol ester-induced NF-jBactivation and COX-2 expression, and induced expression of cytoprotective enzymes in mouse skin *in vivo*.[63] Boeravinone G, a rotenoid compound isolated from *Boerhaavia diffusa* inhibited both TBARS and ROS formation induced by Fenton's reagent, increased SOD activity and reduced $H_2O_2$-induced DNA damage.[64] Additionally, boeravinone G decrease the levels of pERK1 and phospho-NF-kB p65 (but not of pERK2) under stress condition.[64] Curcumin (diferuloylmethane), a bioactive ingredient of *Curcuma longa*, sowed potent anticancer properties in plethora human cancer cell lines/animal carcinogenesis model.[34] Curcumin modulated arsenic induced genotoxicity in human lymphocytes.[65] However, It enhances NK cell-induced apoptosis in pancreatic cancer cells (Fiala, 2015) and inhibits interferon-γ production.[34,66] Additionally, curcumin reduces the hepatotoxicity induced by arsenic, cadmium, chromium, copper, lead and mercury, prevents histological injury, lipid peroxidation and glutathione (GSH) depletion, maintains the liver antioxidant enzyme status and protects against mitochondrial dysfunction.[67] Trans (t)-resveratrol (3,4,5-trihydoxystilbene), present naturally in grapes and other fruits, induces Cdc2-tyr15 phosphorylation via ATM/ATR–Chk1/2–Cdc25C pathway considered as a central mechanism for S phase arrest in human ovarian carcinoma Ovcar-3 cells.[68] Its natural analogue pterostilbene, potently inhibited 7,12-dimethylbenz [a] anthracene (DMBA)/12-O-tetradecanoylphorbol-13-acetate (TPA)-induced mouse skin carcinogenesis.[69] Usnic acid is one of the most common and abundant metabolites found in variety of lichen genera, which are important source of biologically active compounds. It reduces frequencies of micronuclei and DNA damage induced by methyl methane sulfonate in V79 cells.[23] Sinigrin, an abundant glucosinolate of *B. carinata* exhibited an antigenotoxic and anti-tumor activitiesin *Drosophila melanogaster*(SMART) *in vivo* and in HL60 (human promyelocytic leukaemia cell line) systems *in vitro*.[70] Rosmarinic acid, the major phenolic compounds of Salvia sp protected Caco-2 and HeLa cells against genotoxicity of hydrogen peroxide and increased DNA repair activity in Caco-2 cells.[71] Baccharin, the bioactive compounds isolated from the aerial parts of *Baccharis dracunculifolia* inhibits the genotoxic effects of methyl methane sulfonate and hydrogen peroxide in V79 cells.[72] Carnosol, a regular constituent of *Rosmarinus officinalis*, is a phenolic diterpene. It inhibited the invasion of B16/F10 mouse melanoma cells by suppressing the metalloproteinase-9 through down-regulating nuclear factor-kappaB and c-Jun.[73] Carnosol and carnosic acid induced G2/M phase cell cycle arrest by inducing cyclin A and cyclin B1 levels alteration.[74] 6-gingerol, an abundant pungent elements of ginger inhibited cell adhesion, invasion, motility and activities of MMP-2 and MMP-9 in MDA-MB-231 human breast cancer cell lines.[75] 6-Shogaol (alkanone from Ginger) induced apoptotic cell death of human hepatoma p53 mutant mahlavusubline via an oxidative stress-mediated caspase-dependent mechanism.[76] Oligonol, a formulation of catechin-type oligomers, showed inhibitory activity

on phorbol ester-induced tumor promotion and COX-2 expression in mouse skin by targeting NF-jB and C/EBP pathways.[63] Magnolol inhibits the transcriptional activation of iNOS and COX-2 mRNA in mouse skin that is stimulated by TPA. It inhibits the translocation of the nuclear factor-ɤB (NFɤB) subunit and its binding to DNA by blocking the phosphorylation of IɤBR and p65 resulting in the subsequent degradation of IɤBR.[77] Additionally, magnolol can suppress TPA-induced activation of extracellular signal-regulated kinase (ERK)1/2, p38 mitogen-activated protein kinase (MAPK), and phosphatidylinositol 3-kinase (PI3K)/Akt that are involved in tumor migration and invasion.[77] Magnolol inhibited the 7, 12-dimethylbene[a] anthracene(DMBA)/TPA-induced skin tumor formation by reducing the tumor multiplicity, tumor incidence and tumor size of papillomas.[77]

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