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Antioxidants as Functional Foods in Health and Diseases

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Abstract

Antioxidants help protect against oxidation and free radical damage in tissues by neutralizing excess free radicals that eventually induce oxidative stress and degenerative diseases. Many antioxidants are affected by storage, handling and processing, while their combinations may have additive or synergistic effects. Health disorders that are linked to oxidative stress and free radicals include cardiovascular disease, stroke, atherosclerosis, organs ischemia and reperfusion injury, gastrointestinal dysfunctions, cancer, ailments related to AIDS, diabetes mellitus, obstructive sleep apnea, hemorrhagic shock, altered gene expression, hypertension, neurodegenerative diseases (Alzheimer's disease and Parkinson's disease), rheumatoid arthritis, osteoporosis, cataracts and some of functional declines associated with aging. Dietary biophenols are more effective antioxidants in vitro than the antioxidative vitamins. The antioxidants in most functional food (fruits, vegetables, cereals, dry legumes, chocolate, and beverages, e.g. tea, coffee or wine) are due to their phenolic compounds. Epidemiological studies show an inverse relation between myocardial infarction and certain cancer risk with the consumption of certain food.

Keywords: Antioxidants; Sources; Polyphenols; Flavonoids; Degenerative diseases

Introduction

What are antioxidants, Free Radicals, nonradical reactive species and the associated diseases?

Antioxidants are compounds that protect against cell oxidation and free radical damage. Antioxidants neutralize harmful free radicals, and help prevent degenerative diseases. Antioxidant levels in food and their bioavailability may be affected by storage, handling and processing. Different antioxidants may have additive and synergistic effects [1].

Free radicals are molecules with highly reactive unpaired electron. Free radicals, Reactive Oxygen Species (ROS) and reactive nitrogen species (RNS, e.g. nitric oxide, NO) have both deleterious and beneficial effects. Excess free radicals and nonradical reactive species cause oxidative stress, and cell structure changes, including lipids and membranes, proteins, and DNA. Oxidative stress induces either a loss of function, a gain of function, or a switch to a different function in a signaling protein [2].

High ROS levels may come from excess NAD(P)H oxidases stimulation or from mitochondrial electron-transport chain. ROS are undesirable by-products of oxidative energy metabolism in the mitochondria. Medium to low ROS/RNS concentrations are needed to regulate cellular responses to noxia, for example in defence against infections, cellular signalling pathways, and mitogenic response induction. Various ROS-mediated actions protect cells against ROS-induced oxidative stress and re-establish or maintain "redox homeostasis or balance". The physiological functions regulated include vascular tone, signal transduction from membrane receptors, oxygen tension monitoring for controlling ventilation and erythropoietin production [2].

The NO and ROS levels are closely regulated by enzymes such as NO synthase (NOS) and NAD(P)H oxidase isoforms. ROS within cells behave as secondary messengers in intracellular signalling cascades which induce and maintain oncogenic phenotype of cancer cells. However, ROS can also induce cellular senescence and apoptosis, hence can function as anti-tumourigenic species. Chronic oxidative stress and excess free radicals have been implicated in various human diseases. Dietary restriction, metabolic activities, oxygen tension, dietary and pharmacological antioxidants, genetics, affects ROS and human diseases [2].

Health disorders related to oxidative stress and free radicals include cardiovascular disease, stroke, atherosclerosis, organs ischemia and reperfusion injury, gastrointestinal dysfunctions, cancer, ailments linked to AIDS, diabetes mellitus, obstructive sleep apnea, hemorrhagic shock, altered gene expression, hypertension, neurodegenerative diseases (Alzheimer's disease and Parkinson's disease), rheumatoid arthritis, cataracts and some of functional declines associated with aging [3].

What are the best sources of antioxidants?

Polyphenols *vs.* vitamins A, C, E: The antioxidant capacities of most plant products often correlate with their phenolic content. Dietary biophenols are more effective antioxidants in vitro than vitamins E or C. Polyphenols are the most abundant antioxidants in the diet and found in plant products (fruits, vegetables, cereals, dry legumes, chocolate, and beverages, e.g. tea, coffee or wine). Polyphenols (Table 1) have been shown experimentally to prevent cardiovascular diseases, cancers, neuro degeneration, diabetes, or osteoporosis. Epidemiological studies show inverse relation between the risk of myocardial infarction as well as certain cancer risk with the consumption of tea and wine or intake level of some particular flavonoids [4].

Unlike the common synthetic antioxidants (BHA and BHT),

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Table 1: Examples of polyphenols.

Polyphenols	Functions and Rich sources	Sources
Isoflavones and flavonoids	Behave as phytoestrogens with antioxidant properties, and favorable effects on other CVD risk factors, and cancer	Soy, flaxseed oil, whole grains, fruits, and vegetables
Hydroxytyrosol,	A good antioxidant	Olives and olive oil
Lycopene	Antioxidant carotenoid that protects against prostate and other cancers	Tomatoes and other fruits
Resveratrol,	Antioxidant, antithrombotic, anti-inflammatory properties and inhibits carcinogenesis	Nuts and red wine
Curcumin	Anti-inflammatory and modulate gene transcription	Turmeric
Catechins	Anti-obesity, antioxidant	Green tea
Anthocyanins	Antioxidant	Berries
Phlorotannins	Stable potent antioxidants from seaweeds	Seaweeds

many biophenols have prooxidant activity at low concentrations. Compounds with similar structures exhibit comparable trends in antioxidant activity. Antioxidant activities usually increase with increasing number of hydroxyl groups and decrease with glycosylation. The antioxidant activities of many phenolic compounds and plant extracts are comparable to those of synthetic antioxidants [5].

Marine phlorotannins from seaweeds have up to eight interconnected rings, making them 10-100 times more powerful and more stable free-radical scavengers than many other polyphenols (green tea catechins, have only four rings). The half-life of phlorotannins which is partially fat soluble, is up to 12 hours in the body, compared to 30-180 minutes for water-soluble, terrestrial polyphenols, that usually have three interconnected rings (the flavonoids) [6].

Stability

Phenolic compound can be susceptible to extreme pH, high temperatures and enzymes. Drying below 40-50°C yielded the most total phenolics. Drying at room temperature may enhance enzymatic degradation. At high temperatures, certain polyphenol may decompose or combine with the other plant component. Cooking lower the quercetin contents of vegetables with less reduction after frying than after microwaving or boiling. Both boiling and frying causes some loss due to leaching into the cooking water or thermal degradation. Flavonoids glycosides' are fairly stable during normal commercial storage [7].

Flavonoids

Flavonoids (Figure 1) are a class of polyphenols that have diphenylpropanes (C6C3C6) skeleton, and often provide color to fruits, vegetables, wines and beverages. Most flavonoids have potent antioxidant and free-radical scavenging properties and can chelate redox-active metals. Flavonoids occur mainly as glycosides and polymers that are differently degraded in the digestive tract. Enteric absorption and bioavailability occurs sufficiently to reduce plasma oxidant markers. Multiple hydroxyl groups on the molecule confer substantial antioxidant, chelating and prooxidant activity. Methoxy groups introduce unfavorable steric effects and increase the lipophilicity and membrane partitioning. A double bond and carbonyl function in the heterocycle or polymerization of nuclear structure increases the activity by giving a more stable flavonoid radical through conjugation and electron delocalization [8].

Flavonoids are synthesized from phenylalanine, and are ubiquitous. Flavonoids have low toxicity to animal cells and are the constituents of many herbal and insect preparations for medical use, e.g., propolis (bee's glue) and honey. The dietary intake of flavonoids in fruit, beverages, vegetables and seeds, is about 1-2 g. Flavonoids inhibit specific enzymes, simulate some hormones and neurotransmitters, besides scavenging free radicals. The intake of the antioxidant flavonoid normally exceeds that of β-carotene and vitamin E. The total plasma phenol concentration may be higher than predicted due to the presence of metabolites formed in the body's tissues or by the colonic microflora [9]. The average intake of the antioxidant flavonoids was inversely associated with mortality from coronary heart disease.

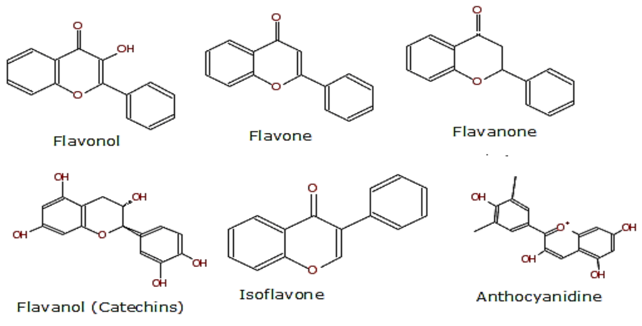

Figure 1: The sub-classes of flavonoids.

Flavonoid Biochemical and Pharmacological Effects

Flavonoids regulate gene expression in plant and animals, and influence many biological functions. Flavonoids have antioxidative, antiinflammatory, anti-platelet aggregation, antiviral, anti-thrombotic, vasodilating and antiallergic effects. Dietary flavonoids have neuroprotective, cardioprotective, and chemopreventive actions. They can inhibit prostaglandin synthase, lypoxygenase and cyclooxygenase, closely relate to tumorigenesis, and induce detoxifying enzyme systems. Flavonols and flavones possess antioxidant and free radical scavenging activity and have significant vitamin C sparing activities, with myricetin, being amongst the most active. Flavonoids increase plasma antioxidant status, have sparing effect on the erythrocyte membrane vitamin E, low-density lipoproteins and polyunsaturated fatty acids [10].

Flavonoids do not act as conventional hydrogen-donating antioxidants but may exert modulatory actions in the cells through actions at protein kinase and lipid kinase signalling pathways.

Table 2: The six major subclasses of flavonoids and their sources.

Flavonoids	Good sources
(i) flavones (e.g., apigenin, luteolin).	broccoli, green chili, bird chili, onion leaves, "belimbi" fruit, "belimbi" leaves, French bean, carrot, tropical celery, Citrus hystrix leaves and dried Garcinium fruit. Chinese cabbage, bell pepper, garlic, French peas, snake gourd, guava, wolfberry leaves
(ii) flavonols (e.g., quercetin, myricetin).	Quercetin inhibited oxidation and cytotoxicity of low-density lipoprotein, and reduce coronary heart disease or cancer risks. Quercetin, myricetin and rutin showed more powerful antioxidant than the traditional vitamins. They protect against cancer, oxidative stress, mutagens, atherosclerosis, suppresses chemopreventive and chemotherapeutic agent, relieve local pain caused by inflammation, headache, oral surgery and stomach ulcer, and inhibits HIV protease activity. They help reduce the mortality from ischemic heart disease, cerebrovascular disease, lung cancer, prostate cancer risk, asthma, and type 2 diabetes risk [12]. Sources: onion, kale, broccoli, French bean and slicing bean. Black tea
(iii) flavanones (e.g., naringenin, hesperidin).	Lowers cerebrovascular disease, asthma. Sources: citrus fruits
(iv) catechins or flavanols (e.g., epicatechin, gallocatechin).	Powerful antioxidants and 20 times more potent than vitamin C. They have the so-called vitamin P effect (regulation of capillary permeability and blood pressure) and anti-obesity properties. Sources: Green tea
(v) anthocyanidins (e.g., cyanidin, pelargonidin).	Oligomericproanthocyanidins, antioxidants is highly bioavailable and provides significantly greater protection against free radicals and free radical-induced lipid peroxidation and DNA damage than vitamins C, E and BETA-carotene. It shows cytotoxicity towards human breast, lung and gastric adenocarcinoma cells, while enhancing growth and viability of normal human gastric mucosal cells. Proanthocyanidins protect against heart, liver and kidney damage by regulating bcl-X(L) gene, DNA damage , against ischemia-reperfusion injury and myocardial infarction in rats by up regulating bcl 2 gene and down regulate oncogene c-myc. Topical application enhances sun protection factor in humans, while supplementation ameliorates chronic pancreatitis in humans. Sources: fruits, vegetables, nuts, seeds, flowers and bark [13].
(vi) isoflavones (e.g., genistein, daidzein).	Prevents oxidation, cancer, through estrogenic/antiestrogenic activity, antiproliferation; induces cell-cycle arrest, apoptosis, detoxification enzymes, regulation of host immune system, and changes in cellular signaling [14]. Sources: Soya, nuts and legumes

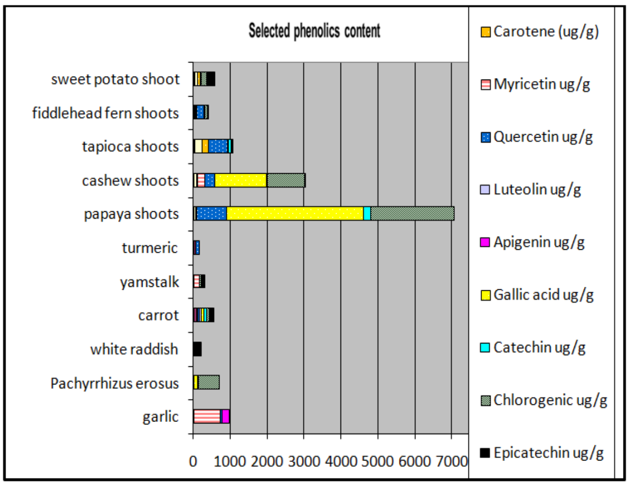

Figure 2: Different Phenolics Content in Edible Plants.

Flavonoids, and their metabolites, act at phosphoinositide 3-kinase (PI 3-kinase), Akt/Protein Kinase B (Akt/PKB), Tyrosine Kinases, Protein Kinase C (PKC), and Mitogen Activated Protein kinase (MAP kinase) signalling cascades. Inhibitory or stimulatory actions at these pathways are likely to affect cellular function profoundly by altering phosphorylation state of target molecules and by modulating gene expression [11]. Flavonoids inhibitor kill many bacterial strains, inhibit important viral enzymes, e.g. reverse transcriptase and protease, and destroy some pathogenic protozoans.

Epidemiological studies show the flavonoid subclasses (flavonols, flavones, catechins and lignans) have positive effects on cardiovascular diseases but not on cancer, with the possible exception of lung cancer [15]. There are over 5000 different known flavonoids that are generally categorized into six major subclasses (Figure 1) (Table 2). Proanthocyanidins (condensed tannins) are complex flavonoid polymers with high molecular weight such as found in black tea and red wine. Proanthocyanidins are good reducing agent and form stable complexes with metal ions and proteins. Proanthocyanidins protect

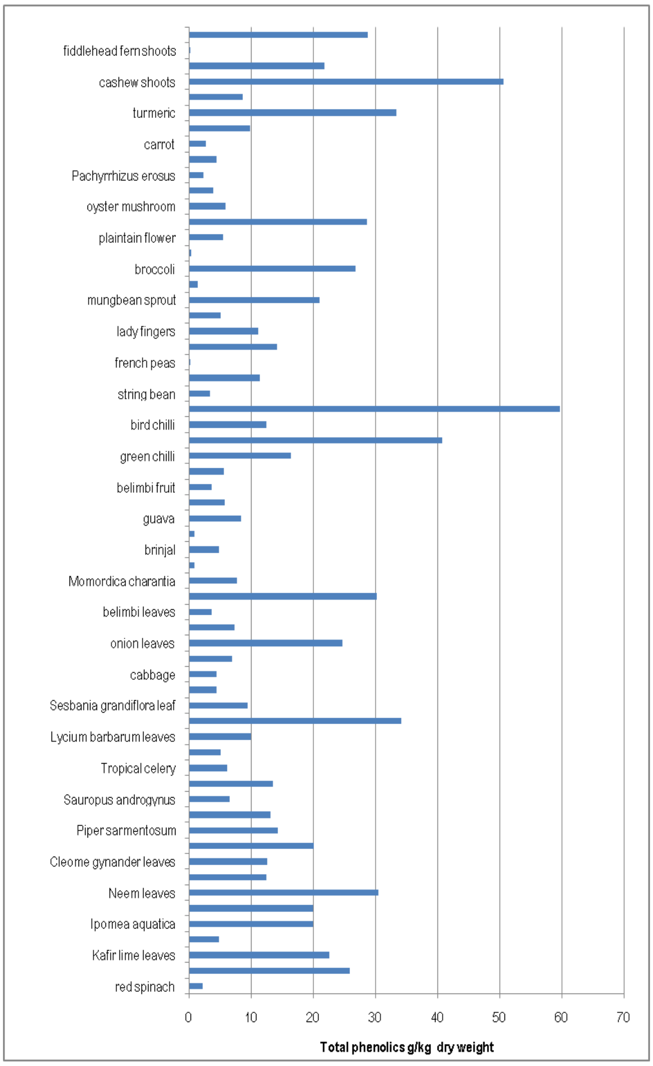

Figure 3: The total phenolic contents of some vegetables and edible leaves.

Table 3: Gallic acid, chlorogenic acid, catechin and epicatechin content in 62 Edible Plants.

Sample **Leafy edible plants**	Gallic acid (ug/g)	Catechin (ug/g)	Cholrogenic(ug/g)	Epicatechin(ug/g)
Red spinach	-	6.0±0.1^{xy}	35.6±0.4^{u}	-
Drumstick leaves	53.7±0.8^{p}	7.8±0.9^{xyw}	10.2±11.7^{w}	-
Citrus hystrix leaves	-	73.3±0.2^{f}	-	-
Pigweed	9.7±0.1^{w}	45.4±4.7^{k}	30.9±1.3^{u}	-
Ipomeareptans	12.4±0.2^{vw}	29.2±0.4^{o}	-	-
Centellaasiatica	-	34.9±0.2^{m}	60.3±0.5st	38.7±0.2^{u}
Neem	9.1±0.2^{w}	24.2±7.2^{oqp}	-	44.2±0.1^{t}
Polygonum. Odoratum	-	75.4±1.0^{f}	-	192.7±0.1^{k}
Cleome gynander	75.1±5.3^{m}	14.0±0.6^{tu}	1263.8±3.0^{d}	70.2±0.1^{q}
Pandan leaves	-	98.6±4.5^{d}	-	3132.1±8.5^{b}
Piper sarmentosum	-	23.5±3.6^{pqr}	3919.0±4.9^{a}	227.4±0.7^{h}
Lemongrass	122.7±0.3^{h}	7.8±0.5^{xyw}	35.8±0.1^{u}	-
Saurapus androgynous	-	0.1±0.1^{z}	-	-
Oenanthejavanica	-	42.4±1.9^{l}	-	-
Apiumgraveolens	-	-	-	-
Mentha spicata	-	-	-	378.2±2.1^{d}
Lyciumbarbarum leaves	149.5±1.4^{g}	-	-	-
Betel leaves	-	-	-	-
Sesbania grandiflora	-	22.3±0.7^{qsr}	-	-
Kai lanBrassica oleracea	112.8±2.8^{i}	22.7±2.8^{qsr}	-	45.6±0.6^{t}
Cabbage Brassica oleracea	201.6±3.0^{e}	16.1±2.2^{t}	-	-
Chinese cabbage B. Rapa	105.6±7.5^{j}	-	-	-
Allium cepa leaves	202.1±2.0^{e}	48.1±1.1^{jk}	828.0±0.8^{f}	186.1±2.0^{l}
Allium tuberosum leaves	-	8.9±0.4^{xvw}	185.0±1.2^{n}	154.2±0.6^{m}
Belimbi leaves	-	48.7±2.3^{j}	183.5±1.6^{n}	530.3±0.6^{c}
Black tea	3345.5±12.7^{b}	4565.9±1.0	642.1±0.9^{h}	4079.0±5.6^{a}
Fruits				
Bitter gourd	71.0±3.0^{n}	6.2±0.8^{xyw}	58.9±1.8st	63.7±0.3^{r}
Pumpkin	15.0±0.6^{v}	22.4±0.8^{qsr}	216.8±2.5^{m}	183.8±0.4^{l}
Brinjal	-	68.9±0.4^{mn}	-	-
Snake gourd	61.4±1.6^{o}	33.2±0.1^{s}	-	-
Guava	120.3±0.8^{h}	-	260.3±2.6^{l}	-
Angular loofah	-	5.1±1.6^{y}	1580.5±0.9^{c}	202.6±2.8^{j}
Belimbi fruit	27.4±3.1^{t}	-	-	-
Garcinia atroviridis	239.0±1.5^{d}	58.4±3.0^{i}	689.1±8.2^{g}	359.9±0.4^{e}
Green chilli	67.6±2.9^{n}	-	-	-
Bell pepper	162.7±2.9^{f}	-	174.5±1.0^{o}	-
Bird chilli	-	-	-	-
Red chilli	111.4±1.9^{i}	-	155.0±0.8^{p}	-
Beans/seeds				
String bean	47.3±1.0^{q}	32.4±0.9^{mn}	73.3±2.3^{r}	258.8±0.9^{f}
Petai	-	-	-	-
French peas	-	-	-	-
French beans	29.5±0.1^{t}	-	-	-
Lady fingers	34.2±0.4^{s}	19.6±1.5^{s}	449.3±6.1^{k}	146.3±0.7^{n}
Soyabean sprout	15.9±0.2^{v}	20.5±0.7^{sr}	18.1±0.7^{r}	-
Mungbean sprout	120.9±1.5^{h}	1.3±0.4^{z}	449.7±4.0^{k}	-
Winged bean	62.9±2.3^{o}	19.8±0.4^{s}	-	-
Flower			-	
Brocoli	21.1±2.1^{u}	-	-	-
Cauliflower	90.3±2.5^{l}	35.2±5.0^{m}	530.7±6.4^{j}	229.5±2.5^{g}
Plaintain flower	-	90.8±0.2^{e}	-	70.9±0.7^{q}
Bungakantan	-	352.2±1.6^{b}	-	357.2±6.4^{e}
Roots				
Garlic	-	-	-	-

Sengkuang	94.7±2.2^{k}	19.9±0.8^{s}	567.8±3.6^{i}	-
White raddish	-	30.7±1.6^{no}	-	127.7±1.4^{o}
Carrot	69.4±3.0^{n}	69.1±1.2^{g}	90.8±1.1^{q}	126.2±0.6^{o}
Yamstalk	-	5.9±0.2^{xy}	63.6±2.1^{s}	93.2±0.5^{p}
Tumeric	-	-	-	-
Shoots				
Papaya shoots	3709.2±0.9^{a}	185.2±4.7^{c}	2248.5±14.4^{b}	-
Cashew shoots	1397.9±0.7^{c}	25.8±0.9^{p}	1010.5±0.8^{e}	22.4±0.8^{v}
Tapioca shoots	23.2±0.2^{u}	63.0±0.6^{h}	-	51.7±0.8^{s}
Fern shoots	0.1±0.2^{x}	9.3±0.8^{vw}	71.6±0.6^{r}	13.1±0.2^{w}
Sweet potato shoot	0.1±0.2^{x}	11.374±6.9^{uv}	156.6±0.4^{p}	215.6±11.1^{i}
Fungi				
Oyster mushroom	41.1±1.4^{r}	29.1±0.5^{o}	57.0±1.2^{t}	42.4±1.1^{t}

Each value is the mean (mg/kg) of three replications ± standard deviation, Means in each column with similar letters are not significantly different (α = 0.05)

against both digestive tract and inner organs cancers; LDLs oxidation, platelet aggregation and cardiovascular diseases [16]. Anthocyanidins strengthen tissues, tendons. Others behave as vasopressor agents (citrus juice, chocolates, and bananas). Limonoids from citrus peels induce phase I and 1l detoxification enzymes in the liver. Flavonoids in various plants (citrus hesperidin; guava-quercetin; buckwheat-rutin) are good for fighting allergies, ulcers, and hepatotoxins.

Vegetables

Spinach, peppers, and asparagus had amongst the highest antioxidant capacity out of 34 vegetables analyzed [17]. Compared to fruits, leaves have higher ORAC values. As leaves become older, ORAC values and total phenolic contents decreased. The total phenolic content is linearly correlated to the ORAC activity for fruits and leaves. Potato peel and beetroot peel extracts showed strong antioxidant effects. In vegetables, quercetin glycosides predominate, but glycosides of kaempferol, luteolin and apigenin are also present [7,18]. Selected phenolics contents of some edible plants are shown in Figure 2 and the total phenolic contents of some vegetables are shown in Figure 3. Table 3 shows the selected phenolics compounds (gallic acid, catechins, chlorogenic acid and Epicatechin contents of 62 fruits and vegetables.

Fruits

Berries (i.e., blackberry, redcurrant and raspberry) had the highest antioxidant properties amongst the fruits [17]. Rosaceae (dog rose, sour cherry, blackberry, strawberry, raspberry), Empetraceae (crowberry), Ericaceae (blueberry), Grossulariaceae (black currant), Juglandaceae (walnut), Asteraceae (sunflower seed) and Punicaceae (pomegranate) too have high antioxidants [19]. Blackberries and strawberries had the highest oxygen radical absorbance capacity, (ORAC) values during green stages, whereas red raspberries had the highest ORAC activity at the ripe stage. The total anthocyanin content linearly correlate to the ORAC values and increased with maturity for many fruits [18]. Table 4 summarizes the major phenolic constituents of various fruits.

Apple varieties may show strong antioxidant activity even though the total phenolic contents are low [21]. Cranberry had highest total phenols, on a fresh weight basis, and was distantly followed by red grape. Ascorbate had only a minor contribution to antioxidants in fruits with exception of melon, nectarine, orange, white grape, and strawberry. The fruit extracts' antioxidant quality was better than the vitamin antioxidants and most pure phenols, suggesting synergism occur among antioxidants in a mixture. Fruits apparently had significantly better quantity and quality of phenol antioxidants than vegetables. Fruits, specifically apples and cranberries, have phenol antioxidants that can protect lower density lipoproteins from oxidation [22]. Cranberry had the highest total phenolic content, followed by apple, red grape, strawberry, pineapple, banana, peach, lemon, orange, pear, and grapefruit. Cranberry showed the highest antiproliferation activities against HepG 2 human liver-cancer cells followed by lemon, apple, strawberry, red grape, banana, grapefruit, and peach [23].

The antioxidant activity of commercial pomegranate juices was three times higher than those of red wine and green tea because they contain the pomegranate tannin punicalagin (1500-1900 mg/L) and hydrolyzable tannins present in fruit rind. Anthocyanins, ellagic acid derivatives, and hydrolyzable tannins were also present in pomegranate juices [24]. Vitamin C in apples contributed less than 0.4% of total antioxidant activity, indicating most of activity comes from natural combination of phytochemicals. Thermal processing elevated total antioxidant activity and bioaccessible lycopene content in tomatoes and produced no significant changes in the total phenolics and flavonoids content [25]. Fruits contain quercetin, kaempferol and myricetin glycosides [7].

Resveratrol (3, 4', 5 trihydroxystilbene) is a naturally occurring phytoalexin produced by some spermatophytes, e.g. grapevines, in response to injury (Figure 4). Resveratrol is present in grape berry skins but not in flesh. Resveratrol has been shown to modulate lipids metabolism, and inhibit low- density lipoproteins oxidation and platelets aggregation. Resveratrol has phytoestrogenic, anti-inflammatory and anticancer properties. Resveratrol has cardioprotective and chemopreventive effects for skin cancer. Resveratrol activates the sirtuin deacetylases and extends life spans [26].

Beverages

Coffee reportedly had amongst the greatest total antioxidant capacity, followed by citrus juices [17]. Tea is rich in catechins, the most active being Epigallocatechin Gallate (EGCG) that function directly and indirectly as antioxidants, on transcription factors and enzyme activities. Beverages like cocoa, coffee, green and black tea contains polyphenols that have health promotion properties and

Table 4: Phenolic constituents of various fruits.

Fruits [20]	Major Phenolic constituents
Bilberry, bog-whortleberry, chokeberry, currants, gooseberry, strawberry, crowberries, roselle and cranberry (most red and bright colourful plant parts)	Anthocyanins
Cowberries	Flavanols, procyanidins
Cloudberry, red raspberry and strawberry	Ellagitannins
Rowanberries	Phenolic acids
Apples	Hydroxycinnamic acids
Pomegranate	Punicalagin, hydrolyzable tannins present in fruit rind
Tomatoes	Lycopene

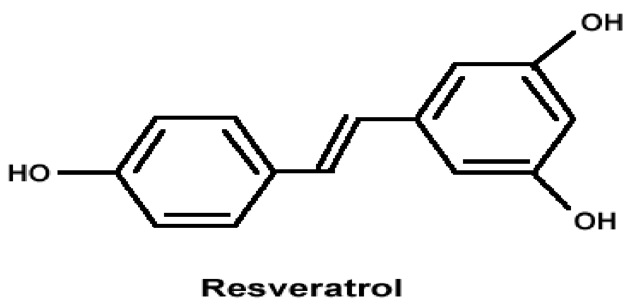

Figure 4: Resveratrol in injured grape skin.

act as antioxidants at cellular levels. They are beneficial for mental performance, cardiovascular health and protect against certain cancer as well as other degenerative diseases [27].

Oils

Soybean oil had amongst the highest antioxidant capacity, followed by extra virgin olive oil, whereas peanut oil was less effective [17]. The red palm oil contains especially high levels of tocotrienols, the pro-vitamin A, carotene and vitamin E to provide good antioxidant, cholesterol-lowering and anticancer properties [28]. Oils from sesame, rice bran, coconuts and other plants are a good source of vitamin E.

Spices

Curcumin (diferuloylmethane) is a polyphenol from plant Curcuma longa, or turmeric. Curcumin has anti-inflammatory, antioxidant, antiproliferative, anti-cancer and antiangiogenic activities. Phase I clinical trials showed it is safe even at high doses (12 g/day) in humans because of its poor bioavailability, due to poor absorption, rapid metabolism, and rapid systemic elimination. Despite this, curcumin has therapeutic efficacy against various human diseases, including cancer, cardiovascular diseases, diabetes, arthritis, neurological diseases and Crohn's disease [29]. Curcumin mechanisms of action include inhibition of several cell signalling pathways at multiple levels, effects on cellular enzymes e.g. cyclooxygenase and glutathione S-transferases, immuno-modulation and effects on angiogenesis and cell-cell adhesion. Curcumin affect gene transcription and induce apoptosis in animal models for cancer chemoprevention and chemotherapy. Although the low systemic bioavailability following oral dosing may limit pharmacological effect in certain tissues, attainment of biologically active levels in gastrointestinal tract has been demonstrated [30].

Ginger (*Zingiberofficinalis*) help prevent against oxidative stress and degenerative diseases mainly through its antiglycating properties and polyol pathway inhibition. Dietary zerumbone from ginger reduced lipid peroxides and enhanced the endogenous antioxidant glutathione level and glutathione reductase activity [31].

Origanummajoricum, O. vulgare ssp. hirtum, and Poliominthalongiflora have higher ORAC and phenolic contents as compared to other culinary herbs. ORAC values and total phenolic content for culinary herbs were much higher than values found in medicinal herbs. Herbs with the highest ORAC values were *Catharanthusroseus*, *Thymus vulgaris*, *Hypericumperforatum*, and *Artemisia annua*. Among identified phenolic compounds, rosmarinic acid was predominant phenolic compound in *Salvia officinalis*, *Thymus vulgaris*, *Origanummajoricum*, and *P. longiflora*, whereas quercetin glucoside and kaempferol glucoside were the predominant phenolic compounds in *Ginkgo biloba* leaves [32]. The essential oil of black cumin seeds, *Nigella sativa L.*, antioxidant activity were from thymoquinone and components carvacrol, t-anethole and 4-terpineol [33].

Seeds

Chia (*Salvia sp*) seeds methanolic and aqueous extracts of defatted chia seeds possessed potent antioxidant activity. The oils had high concentrations of polyunsaturated fatty acids. The major antioxidant activity in nonhydrolyzed extract was caused by flavonol glycosides, chlorogenic acid and caffeic acid. The major antioxidant flavonolaglycones were kaempferol, quercetin and myricetin; and caffeic acid [34].

Medicinal and Aromatic Plants

Salvia sclarea, Salvia glutinosa, Salvia pratensis, Lavandulaangustifolia, Calendula officinalis, Matricariarecutita, Echinacea purpurea, Rhaponticumcarthamoides, Juglansregia, Melilotusofficinalis, Geranium macrorrhizum and *Potentillafruticosa* possessed very high radical scavenging activity [34,35].

Animal or Plant Protein and their Amino Acids

Generally higher protein contents are found in the animal derived food sources, seeds, grains and legumes (10-40% of dry weight dw) compared to the leaves, stems and roots. Based on the biological value, egg and fish is amongst the best source of animal protein and soybean with the protein levels of 35% dw is amongst the best plant protein. Some plants proteins contain all the essential amino acids at levels close to that recommended by FAO/WHO. Many amino acids (Table 5) and peptides have antioxidant and metabolic disease prevention properties [36]. Many plants contain unusual amino acids that may have therapeutic or toxic effects in excess. For example phycobiliproteins from red seaweeds are used as fluorescent markers, and has antioxidant properties which are beneficial for the prevention and treatment of neurodegenerative diseases, cancers, and gastric ulcers [37].

Table 5: Amino acids and their functions for Health.

Amino acids	Functions
Arginine	Nitric oxide precursor, immune system, insulin, liver, liver, collagen
Cysteine and Methionine	Source of sulphur, for skin elasticity, hair, nails, taurine, glutathione antioxidant formation
Phenylalanine converted to tyrosine	To make proteins, brain chemical messengers, dopamine, neurotransmitters epinephrine, norepinephrine
Valine, & isoleucine	Needed for myelin sheath (nerve covering), muscle recovery, hemoglobin, blood-clot formation, & blood sugar regulation
Leucine	Helps regulate blood-sugar, structural tissues (bones, skin and muscles) growth and repair, growth hormone production
Lysine	For antibodies, hormones, enzymes, collagen formation & tissue repair, calcium absorption, nitrogen and ph balance
Tryptophan	For niacin (vitamin B3), serotonin (neurotransmitter for nerve, brain, sleep, moods, pain control, inflammation, intestinal peristalsis) production
Proline	For skin, collagen (hydroxyproline and hydroxylysine), muscles, joints and tendons maintenance
Histidine	Histamine precursor, for immune system, digestive system, blood

Endogenous Antioxidants

Antioxidants and xenobiotics induce gene expression of detoxifying enzymes. Example of the detoxifying enzyme is the Glutathione S-Transferases (GST) that are regulated /induced by xenobiotics and, at least 100 phytochemicals. Many GST inducers effect transcriptional activation of GST genes through Antioxidant-Responsive Element (ARE), Xenobiotic-Responsive Element (XRE), GST P Enhancer 1(GPE), or Glucocorticoid-Responsive Element (GRE) [38]. Small molecules that mimic antioxidant enzymes are becoming new tools for treatment of many diseases.

Some endogenous antioxidants include hormones like melatonin and estrogen that may be up regulated by low intensity stressors e.g. exercise, certain food and dietary restriction [39]. Hormones such as melatonin is highly effective in protecting organisms from oxidative stress and can scavenge up to 10 ROS/RNS even at low concentrations. Melatonin is found in tissues and organs which have high oxygen consumption e.g. brain or are frequently exposed to hostile environmental insults e.g. gut and skin. Another group of endogenous antioxidants are the antioxidant proteins such as the Metallothioneins (MT) that binds to heavy metals and regulate the zinc distribution and levels within cells or organisms. Metallothioneins can also protect against some toxic metals and oxidative stress-inducing agents [40]. The dietary antioxidants may up-regulate the endogenous antioxidants activities, or may down-regulate their activities because of the reduction in their requirements. Either way they work hand in hand to maintain homeostasis and the health of the organism.

Conclusion

Plant antioxidative polyphenols are vasodilatory, anti-inflammatory, anti-fibrosis and antiapoptosis. They activate prosurvival cellular pathways that modulate metabolic intermediates, microRNAs, sirtuins and reperfusion injury salvage kinases and survivor activating factors. The polyphenols improve blood vessels and endothelial cells function by increasing the vasoprotective factors such as Nitric Oxide (NO) and endothelium-derived hyperpolarizing factor, to reduce vascular oxidative stress, hypertension and cardiovascular and degenerative disease risks evidenced by epidemiological studies. Bioactive compounds such as polyphenols, flavonoids, resveratrol, quercetin, epigallocathechin-3-gallate and curcumin, inhibit excessive fat storage, blood pressure, blood glucose, lipid levels, haemoglobin-A1c and insulin resistance in mammals. Polyphenols induce fat breakdown, and retard fat synthesis at molecular level. They protect preadipocytes against mitochondrial changes, obesity-associated diabetes and cardiovascular diseases. Flavonoids are also cardiovascular and cancer protective because they prevent the conversion of galactose to the harmful galactitol.

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