Biogerontology **5:** 275–289, 2004.

Review article

Functional foods, herbs and nutraceuticals: towards biochemical mechanisms of healthy aging

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Received 8 January 2004; accepted in revised form 10 June 2004

Key words: antioxidants, chocolate, DNA oxidation, garlic, ginkgo biloba, lycopene, soy isoflavones, tea, wine

Abstract

Aging is associated with mitochondrial dysfunctions, which trigger membrane leakage, release of reactive species from oxygen and nitrogen and subsequent induction of peroxidative reactions that result in biomolecules' damaging and releasing of metals with amplification of free radicals discharge. Free radicals induce neuronal cell death increasing tissue loss, which could be associated with memory detriment. These pathological events are involved in cardiovascular, neurodegenerative and carcinogenic processes. Dietary bioactive compounds from different functional foods, herbs and nutraceuticals (ginseng, ginkgo, nuts, grains, tomato, soy phytoestrogens, curcumin, melatonin, polyphenols, antioxidant vitamins, carnitine, carnosine, ubiquinone, etc.) can ameliorate or even prevent diseases. Protection from chronic diseases of aging involves antioxidant activities, mitochondrial stabilizing functions, metal chelating activities, inhibition of apoptosis of vital cells, and induction of cancer cell apoptosis. Functional foods and nutraceuticals constitute a great promise to improve health and prevent aging-related chronic diseases.

Free radical-induced damages and subsequent lipid, protein and DNA peroxidations are implicated in many human pathologies (Ferrari 1998; Halliwell 2000). Dietary ingestion of fruits and vegetables or administration of synthetic antioxidants, which neutralize free radicals, could be used to decrease certain chronic diseases of aging (Zhang et al. 1999; Ferrari 2001; Bates et al. 2002).

Healthy dietary practices from ancient Oriental populations originated the concept of functional foods, which enhance body functions and help prevent or even cure dysfunctions and diseases. The influence of Oriental and Mediterranean diets (rich in fruits, vegetables and grains) on cancer and cardiovascular disease morbidity and mortality is remarkable, since those nations present lower total and cardiovascular mortality rates in comparison to the United States, besides their higher *per-capita* intake of alcohol (Weisburger 1999; Trichopoulou and Vassilopoulou 2000). Based on ancient ethnopharmacological knowledge, German physicians usually prescribe herbal medicines to treat common diseases (Wagner 1999) and Japan, China, South Korea and India are leaders in functional food and herbal use and research. In Mediterranean nations, such as Greece, Italy, France, Spain and Portugal, nutritional traditions have been associated with healthy living and aging (Trichopoulou and Vassilopoulou 2000).

The aim of this paper is to review important evidence-based mechanisms of functional foods with special interest on prevention of chronic diseases of aging. Considering limitations of space, it will focus on cardiovascular, neurological and anticarcinogenic properties of functional foods, herbs and nutraceuticals.

Concept of functional foods and nutraceuticals

Functional food has one or more compounds with biochemical and physiological functions beneficial to the human health. The American Dietetic Association has put forward the following definitions (Bloch and Thomson 1995):

- *Chemopreventive agent*: nutritive or non-nutritive food component that has been scientifically investigated as a potential inhibitor of carcinogenesis – green tea polyphenols, resveratrol (grapes/wine); curcumin from indian herb *Curcuma longa*: soy isoflavones; etc.;
- *Functional food*: any altered food or ingredient that could give a beneficial effect beyond that provided by nutrients that traditionally it contains – soy, green tea, nuts, garlic, etc.;
- *Phytochemical*: substances found in edible fruit and vegetables that can be ingested daily (in quantities of grams) by man and that exhibit a potential to modulate human metabolism in favorable mode to prevent cancer and other diseases (added by authors) – isoflavones, resveratrol, garlic allyl-sulphides, tomato lycopene, onion quercetin, etc.; and
- *Nutraceutical*: any substance considered a food or part of this and offers health or medical benefits, including prevention and treatment of diseases – vitamins, minerals (selenium), plants (garlic, ginger, *Ginkgo biloba*), and animal (carnosine, carnitine, chitosan) extracts.

Anti-aging mechanisms of functional foods constituents

By modulating many biological mechanisms in mammalian body and cells, functional foods can exert general health benefits and specific anti-aging benefits.

Based on extensive literature review regarding normal aging and chronic diseases of aging (Ames et al. 1993; Mahoney et al. 2002; Reiter et al. 2002; Driver 2003), it could be proposed the following anti-aging mechanisms of functional foods:

(1) Stabilizers of mitochondrial membranes and enhancers of mitochondrial function, agents that avoid cell death by apoptosis (programmed cell death) or necrosis (accidental cell death).
(2) Metal chelating activities of functional foods.
(3) Antioxidants that decrease cell injury, including those that stimulate antioxidant cell defense systems, protect DNA from oxidation or even inhibit apoptosis of target cells in vital organs.
(4) Inducers of apoptosis of preneoplastic and neoplastic cells.

Aging and mitochondrial diseases

One of the most important sources of reactive oxygen species (ROS) produced by cell respiration is mitochondria (Ames et al. 1993). During life, induced by many pathological stimuli, mitochondrial respiration produces ATP, but releases ROS and other reactive species (from nitrogen and chlorine) that can damage any cell biomolecules. Overproduction of ROS can damage mitochondrial DNA from 4.4- to 48.2-fold than nuclear DNA (Zastawny et al. 1998). This massive oxidative damage to mitochondria is increased during cell aging, affecting mitochondrial DNA and causing mutations that can compromise cell respiration and induce mitochondrial failure (Cottrell et al. 2000). Resistance against mitochondrial failure and free radical damage is determined by efficient antioxidant and repair systems controlled by 'gerontogenes' (Rattan 2003). However, gene mutations or heterozigozity can decrease intracellular antioxidant protection, increasing cell aging and degeneration. In amyotrophic lateral sclerosis (ALS) motor neurons have a SOD-1 mutation that impairs Cu^{+}-binding, causing a failure in the dismutation of molecular oxygen (O_2) to hydrogen peroxide (H_2O_2), with accumulation of superoxide anion (O_2^{-}) (Estevez et al. 1999). This SOD-1 defect also induces senescence in human fibroblasts (Blander et al. 2003). SOD-2 heterozigozity is also associated with decreased capacity to dismutate superoxide and subsequently increasing ROS production, culminating with mitochondrial failure, cell aging and apoptosis (Kokoszka et al. 2001). Mitochondrial failure and massive ROS production is associated with myocardium ischemic injury and aging (Lucas and Szweda 1998; Marín-Garcia and Goldenthal 2002) and with Parkinson's (PD) and Alzheimer's diseases (AD),

both related to decreased glutathione (GSH) content and increasing neuronal apoptosis (Merad-Boudia et al. 1998). Epilepsy, in which occurs the inactivation of mitochondrial aconitase, as a result of massive ROS production, is associated with neuronal loss (Patel 2002). In Wilson's disease, patients suffer from mutations that impair intracellular copper transit, resulting in its toxic accumulation, overproduction of free radicals and mitochondrial DNA mutations linked to premature hepatic aging (Mansouri et al. 1997).

Ku and Sohal (1993) and Barja et al. (1994) reported that aging is not directly linked to higher mitochondrial respiratory activities. In fact, lower rates of superoxide releasing from mitochondria and higher levels of SOD, glutathion peroxidase (GPx) and GSH determine maximum life span. This explains why life span of some organisms could be increased by caloric restriction (Rattan 2003), an anti-aging intervention that decreases breast cancer risk in humans (Michels and Ekbom 2004). Caloric restriction increases *Saccharomyces cerevisiae* life span by activating of sirtuins proteins (silent information regulators), also found in human cells. Howitz et al. (2003) observed that resveratrol from grapes and wine induced sirtuins prolonging *S. cerevisae* life span by 70%. Longevity is inversely associated with higher degrees of polyunsaturated fatty acids in mitochondrial membrane once unsaturation enhances membrane Peroxidation (Pamplona et al. 1998).

The ROS overload caused by increased mitochondrial dysfunction causes opening of mitochondrial membrane channels (mitochondrial pore transition – MPT) releasing cytochrome c, which induces many apoptotic cell death executioner enzymes, the caspases, culminating in apoptosis (Green and Kroemer 1998; Ferrari 2000a, b). Blocking of cytochrome c release by the outer mitochondrial membrane protein Bcl-2 inhibits apoptosis (Kluck et al. 1997; Yang et al. 1997), and decreases superoxide formation increasing survival of neurons (Kane et al. 1993).

Protective pathways of functional foods in mitochondrial diseases

Flavonoids (apigenin, kaempferol, luteolin, myricetin, quercetin), grape/wine polyphenols, vitamin E, chlorophyllin (water-soluble chlorophyll analogue) and other phenols can protect membrane polyunsaturated fatty acids from oxidation, avoiding mitochondrial and other biomembrane disruptions (Brown et al. 1998; Frankel 1999; Terao and Piskula 1999; Boloor et al. 2000). Dietary ω-3 fatty acids improved mitochondrial membrane lipids, decreasing calcium release (apoptosis trigger), and pyruvate dehydrogenase activity (Pepe et al. 1999).

Recently, it was observed that the antioxidant *N*-acetylcysteine prevented Bcl-2 down-regulation increasing cell survival and life span (Kumazaki et al. 2002). However, Bcl-2 overexpression is dangerously linked to oncogenesis, especially if p53 gene had lost its apoptotic capacity (Adams and Cory 1998; Evan and Littlewood 1998).

Beyond Bcl-2, antioxidants modulate mitochondrial function, decreasing cytochrome c releasing and apoptosis. Ebselen, an organoselenium compound, can significantly abrogate apoptosis of myocardial cells exposed to ischemic injury (Maulik et al. 1998). Namura et al. (2001) observed that ebselen decreased cytochrome c releasing and increased survival of stroke-induced brain cells. Selenium deficiency impairs antioxidant defenses by decreasing GPx synthesis, increasing the risk of influenza and coxsackievirus infections, and myocardial injury; but recovery to normal selenium levels decreases infection and protects the heart (Levander 2000; Beck 2001).

Ascorbate/iron-induced lipid peroxidation of brain mitochondrial synaptosomes decreased the levels of ATP, succinate-ubiquinone oxidoreductase (complex II), ubiquinol cytochrome c reductase (complex III), and ATP-synthase activities (complex V), whereas cytochrome c oxidase (complex IV) and NADH-ubiquinone oxidoreductase (complex I) were not affected (Cardoso et al. 1999). Tocopherol, GSH and idebenone abrogated the oxidative decay of complex III, but only GSH blocked complex II and V injuries (Cardoso et al. 1999).

Great attention has been done to melatonin in prevention of oxidative-induced pathologies, since N-acetyl-5-methoxytryptamine is an efficient free radical scavenger and antioxidant (Reiter et al. 2002). Aged rats have decreased brain and plasmatic levels of dopamine, serotonin and some of their metabolites (Lee et al. 2001). Serotonin, a

precursor of the pineal hormone melatonin, controls hypothalamic endocrine secretion, food intake and mood (Castro et al. 2002). In respect of dopamine, its well established that degeneration of dopaminergic neurons from substantia nigra impairs dopamine production and dopamine precursor (L-Dopa) is used to treat PD patients; on contrary to PD, in schizophrenia there is an abnormally production of dopamine and dopamine receptor antagonists are promise in the treatment of this condition (Castro et al. 2002). This means that nutritional-based therapies should be different according to disease-specific targetings. When mitochondrial respiration is decreased, melatonin reversed this pathological condition, specifically increasing complex I and IV activities, stimulating GSH cytoplasmic synthesis, and scavenging many reactive oxygen ($^1O_2$, H_2O_2), nitrogen ($NO^{\bullet}$, $ONOO^-$) and chlorine (HOCl) species (Reiter et al. 2002), especially $OH^{\cdot}$ generated from complex IV (Maurizi 2001). Melatonin reversed alcohol-induced hepatic mitochondrial DNA strand-breaks and massive DNA degradation possibly by its antioxidant actions (Mansouri et al. 1999). Although the anti-aging role of melatonin is far from a consensus, in neurons and cerebrospinal fluid of AD patients melatonin deficiency is usual and its administration recover brain function and improved sleeping, decreasing the burden of disease (Maurizi 2001). Melatonin administration to AD patients improved cognitive functions, decreased nocturnal activity and prolonged sleep period (Asayama et al. 2003). Main food and herbal sources of melatonin are *Scutellaria biacalensis* (Huang-qin), *Hypericum perfuratum* (St. John's wort), *Tanacetum parthenium* (Fever few), *Brassica* sp. (white and black mustard seeds), *Lycium barbarium* (wolf berry seed) and *Trigonella foenum graecum* (fenugreek seed) (Reiter and Tan 2002). However, melatonin supplementation increased both life span and cancer incidence in rats (Anisimov et al. 2001), and had induced atherosclerotic lesions in cholesterol-feed mice (Tailleux et al. 2002).

Coenzyme Q10 (ubiquinone), an electron acceptor of the complex I and II of the respiratory chain, when administered to a mice model of ALS reversed mitochondrial decay and decreased brain striatal damage induced by 3-nitropropionic acid, increasing animal life span (Matthews et al. 1998). Kelso et al. (2001) reported that a mitochondrial targeted ubiquinone compound had the ability to abrogate hydrogen peroxide-induced apoptosis, but not tumor necrosis factor-α induced cell death. Ubiquinone also improves mitochondrial respiration and enhances post-ischemic myocardial contractile function and decreases myocardial damage (Rosenfeldt et al. 2002). Among foods with high coenzyme Q10 content, soy oil (92 mg/100 g), colza seed oil (73 mg/100 g), mackarel fish (43 mg/100 g), sesame seed oil (32 mg/100 g), meat (32 mg/100 g), peanut (27 mg/100 g), pork meat (25 mg/100 g), fish filet (24 mg/100 g), chicken (21 mg/100 g), and nuts (19 mg/100 g) have been noted (Duthie 1993).

L-Carnitine is a mitochondrial membrane fatty acid transporter and stabilizer in aging cells and neurons (Hagen et al. 1998; Binienda 2003; Virmani et al. 2003), enhancing strength and cardio and encephalomyopathies (Mahoney et al. 2002).

Lipoic acid supplementation decreased heart mitochondrial DNA oxidation (Suh et al. 2001), once it has many free radical scavenging activities (Pioro 2000). Caffeine and nicotinamide also showed to protect mitochondria against oxidative stress and dysfunction in a rat model of radiation-induced oxidative damage (Kamat and Devasagayam 2000). Nicotinamide could also decrease free radicals and extend life span (Driver 2003). Carnitine or riboflavin is the treatment choice of rare innate metabolic errors of mitochondrial fatty acid oxidation, that cause muscle and liver damage, vomiting, and cirrhosis, and should be treated during all patient's life (Rinaldo et al. 2002). In aging, increased oxidative stress could worse the citotoxicity of fatty acid disorders, once its accumulation serves as substrates to lipid peroxidation reactions.

Carnosine (β-alanyl-L-histidine), a dipeptide naturally found in mammalian cells (e.g. muscle foods), when present in mice diet decreased brain lipid peroxidation, periophtalmic lesions, skin glossiness, and increased reactivity of a senescence accelerated mice line (Gallant et al. 2000). This dipeptide was also capable to block citotoxicity and formation of protein cross-links and carbonylation induced by malonaldehyde in cultured rat brain endothelial cells (Hipkiss et al. 1997). Carnosine estabilizes mitochondrial structure of stressed cells (Zakharchenko et al. 2003), blocking

the opening of MPT, cytochrome c leakage and subsequent events that leads cell to apoptosis (Kang et al. 2002). It also prolongs life span of human fibroblasts, is cytotoxic to human neoplastic cells (Holliday and McFarland 2000), and inactivates toxic protein carbonyls commonly found in aging cells (Hipkiss 2000) and diabetes (Ferrari 2001).

Metal-chelating activities of functional foods

In Alzheimer's disease, massive iron loading is responsible for neuronal damage though Fenton-derived DNA oxidation and β-amyloid formation (Smith et al. 2000). Zinc and copper are also increased in senile plaques and neuropils of AD patients (Cuajungco et al. 2000). Many drugs with potential to treat neurodegenerative disorders are metal chelators. Some anti-inflammatory/analgesic drugs (aspirin, indomethacin, ibuprofen, d-penicilamine) and antibiotic/antitumor/sedative drugs (bleomycin, ethambutol, thalidomide) chelate copper, iron and zinc; and α-lipoic acid chelates copper, zinc and manganese (Cuajungco et al. 2000). Lipoic acid and dihydrolipoate increases GSH neuronal levels, scavenges hydroxyl, peroxynitrite, nitric oxide, hydrogen peroxide and chelate metals, mechanisms that could be protective against ALS and other neurodegenerative disorders (Pioro 2000). Polyphenols are natural iron chelators with high antioxidant activity (quercetin, rutin, catechins, sesamol, caffeic, ferulic and tannic acids) (Chen and Ann 1998; Lopes et al. 1999; Barnham et al. 2004) that could decrease AD risk. Clioquinol, a metal chelator that cross blood brain barrier, has been successfully used in treatment of AD patients (Barnham et al. 2004).

Antioxidant activities of functional foods: lowering the effects of oxidative stress

Aging impairs mitochondrial function resulting in oxidative imbalance and increase peroxidation biomarkers (lipid, protein, DNA), inducing heat-shock proteins, and depleting antioxidant defense enzymes [catalase-CAT, SOD, GSH, GPx, glutathione-S-transferase] (Lucas and Szweda 1998; Yan et al. 1998; Brack et al. 2000; Hall et al. 2001; Sandhu and Kaur 2002; Rattan 2003).This deleterious phenotype can be reversed by overexpression of SOD and CAT extending life span of *Drosophila melanogaster* and *Caenorhabiditis elegans* (Larsen 1993; Sohal et al. 1995). Higher levels of vitamin A and E were found in human healthy centenarians (Mecocci et al. 2000), reinforcing the antioxidant–life span relationship. Although some studies on antioxidant supplementation have reported positive effects on longevity of organisms results are conflictive. Rather than increasing life span, antioxidants' benefits are related to the control of free radicals that negatively influence healthy aging (Le Bourg 2003), saving antioxidant enzymes and performing the following protective mechanisms:

- Antioxidant gene expression – ginsenoside Rb2 found in panaxadiol (*Panax ginseng* fraction) induced expression of SOD-1 gene, but total saponins and panaxatriol did not affect SOD-1 expression (Kim et al. 1996). Propolis was also able to induce SOD production in rats (Sforcin et al. 1995).
- Protection of LDL cholesterol from oxidation (Frankel 1999).
- Antiapoptotic protection of liver, brain and heart, preserving tissues (Green and Kroemer 1998; Ferrari 2000a, b).

Antioxidants in heart diseases: protection from LDL oxidation

Macrophage cell surface receptors, such as oxidized cholesterol scavenger receptors and lectin-like receptors, recognizes oxidized LDL, promptly phagocyting it and transforming phagocytes in 'foam-like' cells present in earlier atherosclerotic plaques and later atherosclerotic thrombus (Ferrari 1998; Beppu et al. 2001).

Many vitamins can inhibit LDL oxidation, protecting against heart against diseases (Parthasarathy 1999; Ferrari 2001) and the research is seeking for natural compounds that could do the same mechanism (Ferrari and Torres 2002). Preincubation with ascorbic acid, erythorbic acid and dehydroascorbic acid (>10 μm) abrogated macrophage recognition of oxidized mouse erythrocytes, effects better performed by catechins at

levels of 0.01–100 μm (Beppu et al. 2001/. Extra-virgin oil decreased LDL uptake by macrophages and blood oxidized LDL in comparison with refined olive oil. Better performance of extra-virgin oil can be explained by its higher phenolic and α-tocopherol content compared with refined oil (Ramirez-Tortosa et al. 1999). However, Pedersen et al. (2000) reported that olive oil rich diet enhanced blood LDL. Excessive intake could be harmful to cardiovascular health and safety levels are not available yet.

A prospective cohort study performed by Hu et al. (1998) reported that frequent nut consumption decreased coronary heart disease risk by 34%. This could be explained by higher nut content of tocopherols, ω-3 fatty acids and selenium. Anderson et al. (2001) observed that walnut polyphenols inhibit plasma and LDL oxidation. This is the same protective mechanism executed by lycopene-rich foods (tomato juice, spaghetti sauce and tomato oleoresin), fruits and vegetables (β-carotene, A, C and E) and soy isoflavonoids (genistein, daidzein) (Wiseman 1996; Agarwal and Rao 1998; Weisburger 1999; Ferrari 2001). Vitamin C is a promising anti-hypertensive, once its plasmatic levels were inversely associated with arterial blood pressure (Block et al. 2001).

Intake of an isoflavone extract, without soy protein, diminished atherosclerotic lesions of the aorta by 26.3–36.9% (lower and higher supplemented groups, respectively, comparing to control) and decreased the number of positive foam cells (Yamakoshi et al. 2000). Tea ingestion decreased by 23% aortic atherosclerotic injury and decreased aortic cholesterol and triglyceride levels (Miura et al. 2001).

Decreasing the homocysteine factor

Homocysteine, a metabolite from methionine, is an independent cardiovascular disease risk factor, which causes thrombosis and oxidative-stress damage (Durand et al. 2001). It had induced increase blood coagulation and endothelial adhesion molecules, and impaired endothelial responses to arginine, both blocked by vitamin E and C supplementation (Nappo et al. 1999). Higher ingestion of fruit and vegetables (500 g/day) by human subjects was associated with 11% decrease in homocysteine and 15% increase in folate plasmatic levels when compared to the low consumption subject group (100 g/day) (Broekmans et al. 2000). Whole grain intake increases bioavailability of folate and is inversely associated with homocysteine plasma levels, contributing to decrease diastolic blood pressure by their high content of fiber, potassium and magnesium (McKeown and Jacques 2001; McKeown et al. 2002).

Anti-hypertensive and other cardioprotective mechanisms

Functional foods can promote relevant vasodilatory effects by stimulation of nitric oxide production. Beyond inducible effects of ginseng on SOD-1, ginsenosides trigger vascular relaxation by nitric oxide releasing (Couture 2002), and stimulation of calcium–potassium channels and subsequent cascade events of guanylate-cyclase/GMP system (Li et al. 2001), actions that make ginseng a promise to control hypertension. Black tea intake also improved circulation by potent endothelial-dependent dilation of brachial artery in coronary artery disease patients (Duffy et al. 2001).

Psidium guajava (guava) leaves could control hypertension, decreasing myocardial force and inducing atrial relaxation by inhibition of cell inward calcium current (Conde-Garcia et al. 2003), confirming a previous report (Singh et al. 1992).

Quercetin administration (10 mg/kg; during 5 weeks), an onion and garlic flavonoid, to spontaneously hypertensive rats increased antioxidant status and decreased arterial blood pressure and heart rate, without vasodilatory effects (Duarte et al. 2001)

Allicin/ajoene from garlic inhibit macrophage nitric oxide synthase activity decreasing $NO^{\bullet}$ and NOO^{-}, resulting in lesser atherosclerotic effects (Wagner 1999). Atherosclerosis could also be reduced by antioxidants that have inhibited vascular endothelial adhesion molecules, such as VCAM-1 (Fruebis et al. 1999).

Curcumin administration (200 mg/kg) inhibited (30 mg/100g) rat myocardial necrosis, decreasing collagen degradation and re-synthesis, effects mediated by scavenging of free radicals and blocking of lysosomal enzymes releasing (Nirmala et al. 1999). Propolis and grape extracts with high

antioxidant activities blocked myocardial ischemic-reperfusion injuries (Chopra et al. 1995; Cui et al. 2002).

Neuroprotective antioxidants

Higher intake of vegetables and fruits rich in vitamin C and carotenoids was positively associated with better cognitive function in the elderly (Berr 2000). Besides contradictory results of epidemiological studies regarding aging-related dementia and intake of antioxidants (ascorbate, carotenoids, tocopherol), it has been postulated that a rich consumption of fruits and vegetables, plenty of antioxidants, can enhance cognition in the elderly (Youdim and Joseph 2001; Bates et al. 2002). In this manner, phenolic antioxidants such as tocopherols, green tea polyphenols and phytoestrogens (resveratrol and quercetin) decrease oxidative cell injuries and inflammatory reactions, improving brain's health (Erba et al. 1999; Moosmann and Behl 1999; Youdim and Joseph 2001; Bates et al. 2002). Dietary management with aged-garlic extracts, red bell pepper *(Capsicum annuum* L.*)* and lycopene/tomato extracts enhance

Table 1. Antioxidant nutraceuticals, mechanisms against diseases and food sources.

Biomolecules	Mechanisms against disease	Food(s)
Anthocyanins (nasunin), catechins, cyanidins and flavonols	Antioxidant activity by donating electrons and breaking radical-chain reactions; inhibition of LDL oxidation; superoxide scavangers	Grape peels, juice and wine (from red grapes); berries and eggplant
Calcium	Decrease hyperproliferation of colon cancer cells, decreasing the risk of this cancer. Inhibit the activity of ornithine decarboxilase and the ras mutation rate. Promotes the formation of insoluble complexes with bile and fatty acids, decreasing proliferative and irritative effects on intestine	Milk and derivates
Capsaicin	Superoxide anion scavenger	Red and green peppers
Carnosol and carnosoic acid	Inhibit peroxidation of oils	Rosemary extracts
Curcuminoids: diferuloyl methane (curcumin I), *p*-hydroxy cynnamoyl methane (curcumin II), and bis *p*-hydroxy cynnamoyl methane (curcumin III)	Induce GSH, GPx and SOD production; decrease lipid oxidation in liver. Inhibit nitrosative reactions	Turmeric
Daidzein and genistein	Inhibit lipid peroxidation decreasing cardiovascular and cancer's risk;	Soybean and derivatives
Gallic acid, sulfides and thiols	Increase TGF-β signaling pathways involved in blocking G1/S cell cycle transition	Garlic, onion and broccoli
Tocopherol, ubiquinol and tocotrienols	Inhibit peroxidation of lipids and blood cholesterol	Oils (from rice, soy, olive) and fats
Sesaminol (sesame seeds and oil)	Inhibit LDL oxidation and decrease cancer's risk	Rice and rice oil, sesam seeds and sesame oil
Lycopene	Quench singlet oxygen and inhibit LDL oxidation, decreasing the risk of prostate cancer and cardiovascular disease	Vegetables (tomato and greens)
Myricetin and quercetin	Similar to anthocyanins	Same of anthocyanins
Teaflavins (catechin, epicatechin, catechin-gallates, etc)	Inhibit lipid oxidation, decreasing inflammation, atherosclerosis and cancer	Green and black teas

References: Wiseman (1996); Messina et al. (1997); Erba et al. (1999); Frankel (1999); Gann et al. (1999); Haqqi et al. (1999); Krishnaswamy (l999); Lipkin (1999); Ramirez-Tortosa et al. 1999; Kelloff et al. (2000); Louajri et al. (2001).

memory and learning of senescence-accelerated mice (Youdim and Joseph 2001; Suganuma et al. 2002).

Ginkgo biloba

This ancient herb has many pharmacological properties, since blood flow enhancing, decreasing of free radicals production, inhibitory effects on platelet aggregation, protection of striatal dopaminergic system, until inhibition of monoamine oxidase (conserving neurotransmitters in synaptic cavity) (Youdim and Joseph 2001). Egb761 *Ginkgo biloba* extract, which contains quercetin, kaempferol and isorhamnetin as major constituents, was able to remove nitric oxide, increasing survival of hippocampal cells, an effect mediated by its flavonoid group which abrogate Protein Kinase C activation (Bastianetto et al. 2000b). *Gingko biloba* also partially decreased blood free radical production of chronic hypoxic rats (Louajri et al. 2001). Alzheimer's disease patients have massive brain accumulation of an altered protein, the β-amyloid (Smith et al. 2000). It has been reported that Ebg761 *Ginkgo biloba* extract inhibited β-amyloid-induced hippocampal cell death and H_2O_2 production (Bastianetto et al. 2000a). Neuronal cells of the brain cortex of mice supplemented with Ebg761 presented higher expression of growth factors, prolactin (maintain dopaminergic neurons), growth hormone (improves cognition), calcium and chloride protein-channels, neuronal tyrosine/threonine phosphatase 1 (involved in breakdown of the toxic neurofibrilary tangles) and transtyrethin (a hormone transporter and β-amyloid scavenger) (Watanabe et al. 2001). Calcium ion channels trigger axonal membrane depolarization leading to stimulatory neurotransmission, including excitotoxic events; chloride ion channels cause axonal membrane hyperpolarization, which is involved in inhibitory neurotransmission such as performed by glycine and γ-aminobutyric acid (Castro et al. 2002). German physicians have prescribed *G. biloba* for treatment of cognitive dysfunctions, dementia and AD (Wagner 1999). A recent review of randomized human clinical trials with *G. biloba* suggested its utility in dementia and memory impairment therapy (Ernst 2002).

Ginseng

A crude extract from ginseng root inhibited calcium channels, which are implicated in many

Table 2. Antioxidant phytochemicals that prevent DNA oxidant or cancer.

Phytochemical	Mechanism(s)	Food(s)
Cacao polyphenols	Inhibit carcinogen-binding to DNA and DNA oxidation	Cacao, cacao butter and chocolate
Carotenoids (α-and β-carotene, lycopene)	Protect DNA from oxidation	Apples, tomato, color fruits and green vegetables
Curcuminoids	Inhibit carcinogen-binding to DNA, DNA oxidation and increase DNA repair	Turmerici
Genistein	Stabilizes protein-DNA links	Soybean
Garlic and onion thiols	Inhibit carcinogen-binding to DNA and DNA oxidation	Garlic and onion
Myricetin, quercetin and rutin	Inhibit DNA oxidation by direct scavenger actions	Teas, grapes and wines
Tannic acid	Inhibit mutagenesis and carcinogenesis through iron-chelating activities	Plants

References: Wiseman (1996); Dreosti (1998); Frankel (1999); O'Brien et al. (2000); Sato and Miyata (2000); Trichopoulou and Vassilopoulou (2000) ; Yamagishi et al. (2000); Ferrrari (2001).

Table 3. Food phytochemicals that induce apoptosis and contribute to cancer control.

Phytochemical	Target cancer cells	Food source	Reference
Artellipin C	Human leukemia cells	Brazilian propolis	Kimoto et al. (1998)
Butyrate	Colon cancer cells	Vegetable fibers	Chapkin et al. (2000)
Catechins	Various cancer cells	Teas	Yang et al.(l998)
Flavonoids (epigalocatechin/ genistein)	Transformed human breast cells	Teas, soy, fruits and vegetables	Katdare et al. (1999)
Indole-3 -carbinol (phytoalexin)	Transformed human breast cells human mammary cells	Cruciferae vegetables	Katdare et al. (1999)
Isoprenoids, terpenoids and tocotrienols (vitamin E-related compounds)	Melanoma cells and transformed or malignant human breast cancer cells	Vegetable oils; nuts and seeds	He et al. (1997) Katdare et al. (1999); Nesaretnam et al.(1998)
Isothiocyanates	Many cancer cells	Cruciferae (broccoli)	Chen et al.(l998)
Fish oil fats	Increase colon cell differentiation and apoptotic rates, inhibiting azoxymethane-induced colon cancer	Fish oil	Chang et al. (1998)
Retinoids (vitamin A-related)	Many tumors, including breast cancers	Vitamin A rich foods (oils, dark green leaf vegetables and fruits)	Katdare et al. (1999); Lippman and Lotan (2000)
Polyphenols	Human lymphoic leukemia cells	Persimmon (*Diospyros kaki*); green teas, wine, etc	Achiwa et al. (1997)
Protopanaxadiol	HL-60 cells	Ginseng metabolite from ginsenosides Rbl,Rb2 and Rc	Lee et al. (2000)
Sulphides	Gastrointestinal and other cancer cells	Garlic (allyl-sulphides)	Knowles and Millner (2001)

neuronal death pathways (Ferrari 2000a), and had similar properties to opioids (Nah et al. 1995). Ginseng increases antioxidant expression (Kim et al. 1996), induces vascular relaxation and hypotensive effects (Li et al. 2001; Couture 2002), which can benefit neurovascular domains, improving memory in animals (Youdim and Joseph 2001), but clinical trials do not support its therapeutic use in human (Ernst 2002). Important functional foods and their protective effects are grouped in Table 1.

Anticancer activities

Functional food biomolecules can exert anticarcinogenic effects through diverse pathways. Modulation of cytochrome P_{450} enzymes, antioxidant protection of DNA, and induction of apoptosis of cancer cells constitute the most important anticancer mechanisms of functional foods. Increasing DNA repair (folic acid); changing immunological response (carotenoids, vitamins C and E, selenium and zinc); inhibition of cyclooxygenase (resveratrol); restriction of caloric intake and absorption; decreasing time for transit of intestinal bulk, avoiding carcinogen formation and absorption (fibers); inhibition of angiogenesis; and abrogation of tumor cells proliferation (by suppressing telomerase or induction of apoptosis) also constitute important anticancer properties of functional foods (Halliwell 1999; Kelloff et al. 2000; Ferrari and Torres 2003).

During life span there is an enhancement of body free radical production, which is associated with oxidative DNA damage and increased risk of cancer (Dreosti 1998; Ferrari and Torres 2003). Tocopherols, carotenoids (from fruits such as apples) and lycopene can decrease cancers' risk (Ferrari 2001). Many compounds from functional foods could suppress DNA oxidation (Dreosti 1998; Biasco and Paganelli 1999; O'Brien et al. 2000; Yamagishi et al. 2000) (Table 2).

Apoptosis, a genetic cell death program, is important to kill undesirable cells (old, degenerated and oncogenic), avoiding inflammatory reactions (Ferrari 2000a, b), Some important chemopreventive agents able to induce apoptosis are listed in Table 3.

Discussion and conclusion

Although observational and experimental research support the protective roles of functional foods against chronic diseases, negative results pointed the urgence for more research regarding establishment of efficacy and safety parameters. For example, although soy genistein could decrease mammary cancer risk by blocking cytochrome P_{450} xenobiotic metabolism, pharmacological antagonism of estrogen-receptors, increasing mammary cancer cell apoptosis, blocking progression through the G1/S cell cycle phase and antioxidant protective mechanisms (Wiseman 1996; Messina et al. 1997; Katdare et al. 1999; Kelloff et al. 2000), some clinical studies demonstrated that soy genistein and daidzein could augment breast cancer, especially in women with previous history of this cancer (Lemos 2001). Postmenopausal women treated with iproflavone (200 mg/day) had not bone mass gains, but lymphocyte counting was depleted in 13% of patients (Alexandersen et al. 2001). In this regard, according to Mahoney et al. (2002) no clinical controlled trials testing mitochondrial enhancers were published yet. Then, critical thinking on use of foods is essential, since they can fail or induce adverse effects, and a real pharmacological approach is needed to consolidate functional food science against fallacious reports.

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