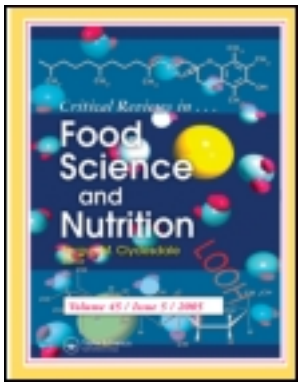

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Dietary Intake of Natural Antioxidants: Vitamins and Polyphenols

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Dietary Intake of Natural Antioxidants: Vitamins and Polyphenols

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Oxidative stress is a condition in which oxidant metabolites exert their toxic effect because of an increased production or an altered cellular mechanism of protection; oxidative stress is rapidly gaining recognition as a key phenomenon in chronic diseases. Antioxidants terminate these chain reactions by removing free radical intermediates, and inhibit other oxidation reactions by being oxidized themselves. Endogenous defence mechanisms are inadequate for the complete prevention of oxidative damage, and different sources of dietary antioxidants may be especially important. This article calls attention to the dietary antioxidants, such as vitamins A, C, and E and polyphenols. Compelling evidence has led to the conclusion that diet is a key environmental factor and a potential tool for the control of chronic diseases. More specifically, fruits and vegetables have been shown to exert a protective effect. The high content of minerals and natural antioxidant as vitamins A, C, and E and polyphenols in fruits and vegetables may be a main factor responsible for these effects.

Keywords Antioxidant, food, vitamin A, vitamin C, vitamin E, polyphenols, health

INTRODUCTION

Oxidative stress, the consequence of an imbalance of pro-oxidants and antioxidants in the organism, is rapidly gaining recognition as a key phenomenon in chronic diseases (Dhalla et al., 2000; Moylan and Reid, 2007). A particularly destructive aspect of oxidative stress is the production of reactive oxygen species, which include free radicals and peroxides. A free radical is any atom or molecule that has a single unpaired electron in an outer shell. While a few free radicals such as melanin are not chemically reactive, most biologically-relevant free radicals are highly reactive (Jennings et al., 2009).

The range of antioxidant defences available within the cell and extracellular should be adequate to protect against oxidative damage. However, the balance can be lost because of overproduction of free radicals by exposure to sources that overwhelm the antioxidant defences, or by inadequate intake of nutrients that contribute to the defence system (Valko et al., 2007).

All forms of life maintain a reducing environment within their cells. This reducing environment is preserved by enzymes that maintain the reduced state through a constant input of metabolic energy. Disturbances in this normal redox state can cause toxic effects through the production of peroxides and free radicals that damage all components of the cell, including proteins, lipids, and DNA (Valko et al., 2007). Low levels of antioxidants, or inhibition of the antioxidant enzymes, cause oxidative stress and may damage or kill cells.

Prime targets for free radical reaction are the unsaturated fatty bonds in membrane lipids (Pamplona 2008. Consequent peroxidation results in a loss in membrane fluidity and receptor alignment and potentially in cellular lysis. Free radical damage to sulfur-containing enzymes and other proteins culminates in inactivation, cross-liking and denaturation (Davies et al., 1987). Nucleic acids can be attacked and subsequent damage to the DNA can cause mutation that may be carcinogenic. Oxidative damage to carbohydrates can alter any of the cellular receptor functions including those associated with hormonal and neurotransmitter responses. Free radicals such as peroxy radicals, the superoxide anion, and the hydroxyl radical are responsible for many of the damaging reactions (Pamplona 2008). In addition, certain aldehydes such as malondialdehyde and hydroxynonenal, arising from the free radical degradation of polyunsaturated fatty acids, can cause cross-linking in lipids, proteins, and nucleic acids (Dalle-Donne et al., 2006).

In humans, oxidative stress is involved in many diseases, such as atherosclerosis (Schwartz et al., 2009; Jenner and

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Jenner, 2009), heart failure (Ferrari et al., 2004), myocardial infarction (Sartório et al., 2007), Alzheimer's disease (Butterfield et al., 2006), fragile X syndrome (El Bekay et al., 2007), and chronic fatigue syndrome (Chung et al., 2009). The free-radical theory of aging states that organisms age because cells accumulate free radical damage over time (Ashok and Ali, 1999). Mammalian cells have developed highly protective inducible systems against a variety of stressful stimuli, including oxidative challenges. When appropriately activated, each one of these systems has the potential to restore cellular homeostasis and rebalance redox equilibrium (Li et al., 2002). Activation of antioxidant pathways is particularly important for tissue with relatively weak endogenous antioxidant defences, such as the brain (Calabrese et al., 2001). Increasing evidence, in fact, supports the notion that reduction of cellular expression and activity of antioxidant proteins and consequent augmentation of oxidative stress are fundamental causes for aging processes and neurodegenerative diseases (Li et al., 2002; Calabrese et al., 2003).

Compelling evidence has led to the conclusion that diet is a key environmental factor and a potential tool for the control of chronic diseases. Dietary recommendations for the prevention of cancer, atherosclerosis, and other chronic diseases have been established by various health agencies. More specifically, fruits and vegetables have been shown to exert a protective effect (Joshipura et al., 1999; Cox et al., 2000; Strandhagen et al., 2000). The high content of vitamins A, C, and E and polyphenol antioxidants in fruits and vegetables may be a main factor responsible for these effects (Vinson et al., 2001; 2002; Blomhoff et al., 2006).

Although some of the health benefits of fruits and vegetables have been attributed to their content of polyphenols and vitamins, the specific mechanisms by which these compounds affect human health remains unclear, despite extensive research conducted in this area in recent years. Most of the researches have focused on the antioxidant properties of flavonoids, which are well characterized and well established in vitro (Kris-Etherton et al., 2004; Lolito and Frei, 2006). However, the in vitro data often conflict with results from in vivo studies on the antioxidant capacity of plasma or the resistance of plasma and lipoproteins to oxidation ex vivo after the consumption of flavonoid-rich foods by human subjects (Finley, 2005). These inconsistencies between the in vitro and the in vivo data are likely explained by the limited bioavailability of dietary flavonoids and their extensive metabolism in humans (Carbonaro et al., 2001; Scalbert and Williamson, 2000; Manach et al., 2004).

This article calls attention to the dietary antioxidants, such as vitamins and polyphenols. As discussed, endogenous defence mechanisms are inadequate for the complete prevention of oxidative damage, thereby making sources of dietary antioxidants especially important.

ANTIOXIDANTS

An antioxidant is a molecule capable of slowing or preventing the oxidation of other molecules (Halliwell, 1990). As above mentioned, the oxidation reactions can produce free radicals, which start chain reactions that damage cells. Antioxidants terminate these chain reactions by removing free radical intermediates, and inhibit other oxidation reactions by being oxidized themselves (Genestra, 2007). Although oxidation reactions are crucial for life, they can also be damaging; hence, animals maintain complex systems of multiple types of dietary antioxidants, such as vitamin A, vitamin C, vitamin E, and polyphenols (Kalpakeioglu and Senel, 2007; Yoo et al., 2008). Moreover, although the minerals zinc, manganese, copper, selenium, and iron have been considered as antioxidants, really they are not, though they are essential for antioxidant enzyme activity (Zuo et al., 2006). Several trace elements protect the cell from oxidative cell damage by incorporating into antioxidant enzymes. Zinc, copper, and manganese are required for superoxide dismutases in both cytosol and mitochondria (Fujimora et al., 2000). Selenium is an essential component of glutathione peroxidases and iron is a constituent of catalase, a hemeprotein, which catalyzes the decomposition of hydrogen peroxide (Machlin and Bendich, 1987).

VITAMINS AND ANTIOXIDANT ACTIVITY

Vitamin A is a fat-soluble vitamin. Structurally similar to vitamin A, carotenoids are a group of nearly 600 compounds. Only about 50 of these have provitamin A activity. Antioxidant activity has been reported for vitamin A_1 (retinol) (Figure 1) and A_2 (dehydroretinol) as well as for many pro-vitamin A compounds, including β- and α-carotenes. Other similar carotenoid molecules with little or no vitamin A activity, but that are found in substantial quantities in the human diet and in tissues, are also reported to have antioxidant activity (e.g., lycopene, lutein, canthaxanthin, neoxanthin, violaxanthin, astaxanthin and zeaxanthin) (Olson 1998).

Vitamin A must be obtained from the diet and it is found naturally in many foods such as liver, carrot, broccoli, sweet potato, butter, kale, spinach, pumpkin, collard greens, cheddar cheese, cantaloupe melon, egg, apricot, papaya, mango, pea, and milk (Holden et al., 1999) (Table 1).

A recommended dietary intake (RDI) of 700 μg and 600 μg of vitamin A was suggested for nearly all referenced men and women, respectively (Olson 1987. The recommended dietary allowance (RDA) for vitamin A has been established in 700 μg/day for women and 900 μg/day for men in the US, primarily based on biochemical evidence (www.iom.edu) (Table 1).

Within the body, vitamin A can be found as retinol, retinal and retinoic acid. Because all of these forms are toxic at

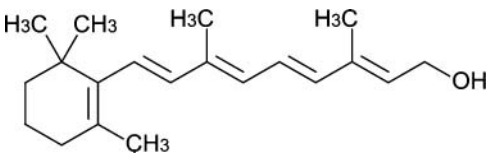

Figure 1 The structure of retinol, the most common dietary form of vitamin A.

Table 1 Foods with high content of antioxidants (vitamin A, C, E and polyphenols) and the recommended dietary allowed (RDA)

	Foods	RDA
Vitamin A	Liver, carrot, broccoli, sweet potato, butter, kale, spinach, pumpkin, collard greens, cheddar cheese, cantaloupe melon, egg, apricot, papaya, mango, pea, broccoli, and milk	700–900 μg/day
Vitamin C	Broccoli, bell peppers, kale, cauliflower, strawberries, lemons, mustard and turnip greens, brussels sprouts, papaya, chard, cabbage, spinach, kiwifruit, snow peas, cantaloupe, oranges, grapefruit, limes, tomatoes, zucchini, raspberries, asparagus, celery, pineapples, lettuce, watermelon, fennel, peppermint, and parsley	75–90 mg/day
Vitamin E	Asparagus, avocado, egg, milk, nuts, seeds, spinach, asparagus, wheat germ and wholegrain foods	15 mg/day
Polyphenols	Berries, tea, beer, grapes/wine, olive oil, chocolate/cocoa, coffee, walnuts, peanuts, borojo, pomegranates, popcorn, yerba mate, and other fruits and vegetables	—

high concentrations, they are bound to proteins in the extracellular fluids and inside cells (Palace et al., 1999). Vitamin A is stored primarily as long chain fatty esters and as provitamin carotenoids primarily in the liver, kidney, and adipose tissue (Debier and Larondelle, 2005).

The antioxidant activities of vitamin A and carotenoids are conferred by the hydrophobic chain of polyene units that can quench singlet oxygen, neutralize thiyl radicals, and combine with and stabilize peroxyl radicals. In general, the longer the polyene chain, the greater the peroxyl radical stabilizing ability (Galano, 2007). Because of their structures, vitamin A and carotenoids can auto-oxidize when O_2 tension increases, and thus are most effective antioxidants at low oxygen tensions that are typical of physiological levels found in tissues (KrinsKy and Johnson, 2005).

Vitamin C or L-ascorbic acid (Figure 2) is an essential nutrient for humans and certain other animal species, in which it functions as a vitamin (Benzie, 1999). Ascorbate (an ion of ascorbic acid) is required for a range of essential metabolic reactions in all animals and plants. In living organisms, ascorbate is an antioxidant, since it protects the body against oxidative stress, and is a cofactor in at least 8 enzymatic reactions, including several collagen synthesis reactions that cause the most severe symptoms of scurvy when they are dysfunctional (Padh, 1991).

Excellent food sources of vitamin C include broccoli, bell peppers, kale, cauliflower, strawberries, lemons, mustard and turnip greens, Brussels sprouts, papaya, chard, cabbage, spinach, kiwifruit, snow peas, cantaloupe, oranges, grapefruit, limes, tomatoes, zucchini, raspberries, asparagus, celery, pineapples, lettuce, watermelon, fennel, peppermint, and parsley (Lee and Kader, 2000; García-Closas et al., 2004) (Table 1).

Carr and Frei (1999a) suggested that an intake of 90–100 mg vitamin C per day is required for optimum reduction of chronic disease risk in nonsmoking men and women, suggesting a recommended dietary allowance (RDA) for vitamin C of 120 mg vitamin C per day. Nevertheless, the RDA for vitamin C has been established in 75 mg/day for women and 90 mg/day for men in the US, primarily based on biochemical evidence (www.iom.edu) (Table 1).

Vitamin C is an effective antioxidant for several reasons. First, both ascorbate and the ascorbyl radical, the latter formed by one electron oxidation of ascorbate, have low reduction potentials and can react with most other biologically relevant radicals and oxidants (Carr and Frei, 1999b). Second, the ascorbyl radical has a low reactivity due to resonance stabilization of the unpaired electron, and readily dismutates to ascorbate and dehydroascorbic acid (DHA) (Carr and Frei, 1999b). In addition, ascorbate can be regenerated from both the ascorbyl radical and DHA by enzyme-dependent and independent pathways. The ascorbyl radical is reduced by an NADH-dependent semidehydroascorbate reductase and the NADPH-dependent selenoenzyme thioredoxin reductase. DHA can be reduced back to ascorbate nonenzymatically by GSH and lipoic acid as well as by thioredoxin reductase and the GSH-dependent enzyme glutaredoxin.

Ascorbic acid behaves not only as an antioxidant but also as a pro-oxidant (Carr and Frei, 1999b). Ascorbic acid has been shown to reduce transition metals such as cupric ions (Cu^{2+}) to cuprous (Cu^{1+}) and ferric ions (Fe^{3+}) to ferrous (Fe^{2+}) during conversion from ascorbate to dehydroxyascorbate in vitro. This reaction can generate superoxide and other reactive oxygen species. However, in the body, free transition elements are unlikely to be present while iron and copper are bound to diverse proteins.

Vitamin E is the term for a group of tocopherols and tocotrienols, of which α-tocopherol has the highest biological activity (Figure 3). Vitamin E is a fat-soluble antioxidant that stops the production of reactive oxygen species formed when fat undergoes oxidation (Traber and Atkinsom, 2007). Due to the potent antioxidant properties of tocopherols, α-tocopherol

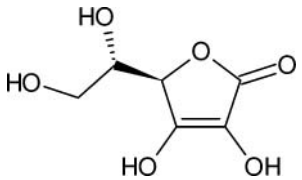

Figure 2 Vitamin C or L-ascorbic acid.

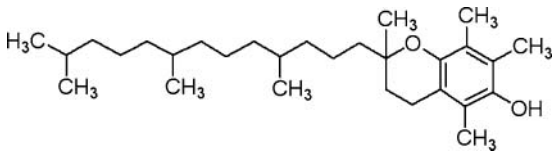

Figure 3 The α-tocopherol form of vitamin E.

has been most studied as it has the highest bioavailability (Roy et al., 2002). The impact of tocopherol in the prevention of chronic diseases believed to be associated with oxidative stress has often been studied, and beneficial effects have been demonstrated (Willcox et al., 2008).

Particularly high levels of vitamin E can be found in the following foods: asparagus, avocado, egg, milk, nuts, seeds, spinach, asparagus, wheat germ, and wholegrain foods (McLaughlin and Weihrauch, 1979; García-Closas et al., 2004). The RDA for vitamin E has been established in 15 mg/day for women and men (www.iom.edu) (Table 1).

Traber and Atkinson (2007) propose the hypothesis that all of the observations concerning the in vivo mechanism of action of α-tocopherol result from its role as a potent lipid-soluble antioxidant. The importance of this function is to maintain the integrity of long-chain polyunsaturated fatty acids in the membranes of cells and thus maintain their bioactivity. That is to say that these bioactive lipids are important signaling molecules and that changes in their amounts, or in their loss due to oxidation, are the key cellular events that are responded to by cells. The various signaling pathways that have been described to be under α-tocopherol regulation appear rather to be dependent on the oxidative stress of the cell or tissue under question.

POLYPHENOLS AND ANTIOXIDANT ACTIVITY

Polyphenols are a group of chemical substances found in plants, characterized by the presence of more than one phenol unit or building block per molecule (Bravo, 1998) (Figure 4). Phenolic compounds are currently receiving much attention because of their beneficial health effects related to their antioxidant (Vinson et al., 2005; Dehkharghanian et al., 2009), anti-inflammatory (Tipoe et al., 2007; Nichols and Katiyar, 2010), cardioprotective (Zern and Fernandez, 2005), cancer chemopreventive (Nichols and Katiyar, 2010; Castillo-Pichardo et al., 2009), and neuroprotective properties (Stevenson and Hurst, 2007; Aquilano et al., 2008).

In nature, phenolics are usually found conjugated to sugars and organic acids and can be classified into two major types: flavonoid and nonflavonoid phenolics. All flavonoid phenolics share a basic structure consisting of two benzene rings linked through a heterocyclic pyrone C ring. In contrast, nonflavonoid phenolics include a more heterogeneous group of compounds including from the simplest of the class such as C6-C1 benzoic acids and C6-C3 hydroxycinnamates to more complex compounds such as C6-C2-C6 stilbenes, C6-C3- C3-C6 lignans and hydrolyzable tannins, gallotannins, and ellagitannins, with the principal component being gallic acid and hexahydroxydiphenic acid that upon hydrolysis releases ellagic acid (Bravo, 1998).

Polyphenols present in food can help limit the oxidative damage and acting directly on reactive oxygen species or by stimulating endogenous defence systems (Förstermann, 2008). The phenolic groups in polyphenols can accept an electron to form relatively stable phenoxyl radicals, there by disrupting chain oxidation reactions in cellular components. The efficiency of polyphenols as antioxidant compounds greatly depends on their chemical structure (Cotelle, 2001). Phenol itself is inactive as an antioxidant, but *ortho*- and *para*-diphenolics have antioxidant capacity, which increases with the substitution of hydrogen atoms by ethyl or *n*-butyl groups. Flavonoids are among the most potent plant antioxidants because they possess one or more of the following structural elements involved in the antiradical activity**:** (1) an *o*-diphenolic group (in ring B), (2) a 2–3 double bond conjugated with the 4-oxo function, and (3) hydroxyl groups in positions 3 and 5. Quercetin (Figure 4), a flavonol that combines all of these characteristics, is one of the most potent natural antioxidants. Also, the antioxidant efficiency of flavonoids is directly correlated with their degree of hydroxylation and decreases with the presence of a sugar moiety (glycosides are not antioxidants, whereas their corresponding aglycones are antioxidant) (Bravo, 1998; Cotelle, 2001).

DIETARY POLYPHENOLS AND BIOAVAILABILITY

Notable sources of polyphenols include berries, tea, beer, grapes/wine, olive oil, chocolate/cocoa, coffee, walnuts, peanuts, borojo, pomegranates, popcorn, yerba mate, and other fruits and vegetables (Vinson et al., 2001; Vinson et al., 2003) (Table 1). Polyphenols preparations are also available as dietary supplements.

The main dietary sources of polyphenols are fruits and beverages. Fruits like apple, grape, pear, cherry, and various berries contain up to 200–300 mg polyphenols per 100 g fresh weight. Typically, a glass of red wine or a cup of tea or coffee contains about 100 mg polyphenols. Cereals, chocolate, and dry legumes also contribute to the polyphenol intake. Dietary intake of polyphenols has been estimated about 1 g/day (Scalbert and Williamson 2000) and represents approximately two-thirds of the total daily phenolic intake, with approximately one third as phenolic acids. It is much higher than that of all other known dietary antioxidants, about 10 times higher than that of vitamin C and 100 times higher than those of vitamin E and Vitamin A (Scalbert et al. 2005b). The most abundant types of polyphenols found in diet are the flavonoids, most often conjugated as glycosides. More than 4000 chemically unique flavonoids have been identified in plants, particularly fruits, vegetables, nuts, seeds, and flowers, as well as in several beverages, delivering a complex mixture of polyphenols and phenolic acids to our gastrointestinal tract. The polyphenols in wine include phenolic acids, anthocyanins, tannins, and other flavonoids (Alonso et al., 2002). Tea is the second most commonly consumed beverage worldwide and has been shown to contain high concentrations of flavanols such as epicatechin, catechin (Figure 4) and their gallate esters, epigallocatechin, gallocatechin, epicatechin gallate, and epigallocatechin gallate (Wiseman et al., 2001).

Recommended dietary allowance (RDA) values exist for vitamins and provide a guideline on the optimal dose range to avoid deficiency and prevent toxicity. However, there are still

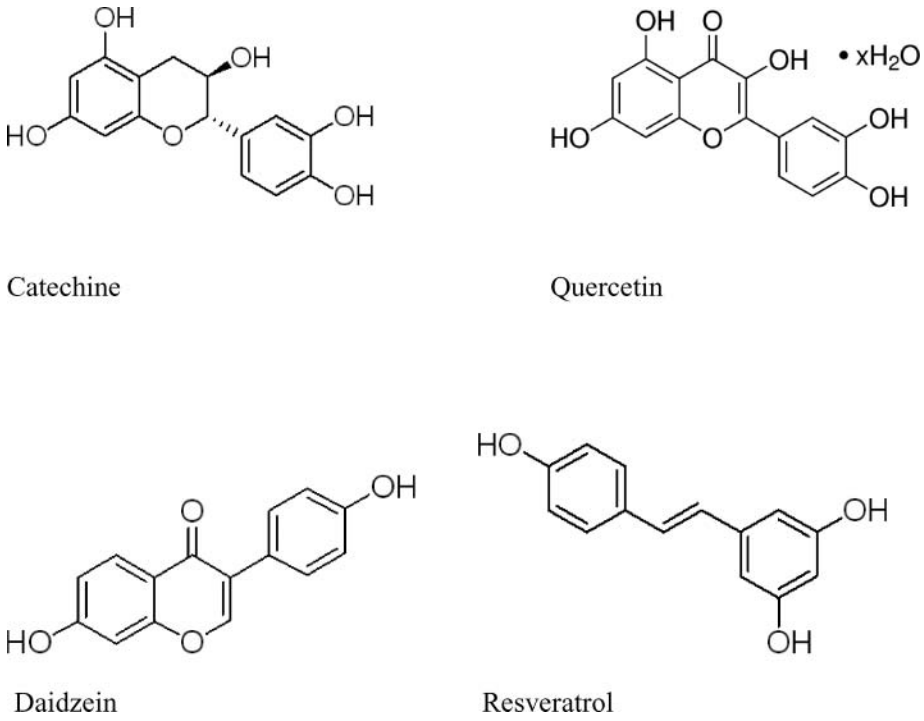

Figure 4 The structure of polyphenols: Catequine, quercetin, daidzein and resveratrol.

many gaps in our knowledge and there is a large number of structurally different polyphenols which may be relevant for health, and obtaining enough information to set an RDA for each of these will not be feasible in the foreseeable future (Williamson and Holst, 2008)

The maximum concentration in plasma rarely exceeds 1 mM after the consumption of 10–100 mg of a single phenolic compound. However, the total plasma phenol concentration is probably higher due to the presence of metabolites formed in the body's tissues or by the colonic microflora (Scalbert and Williamson, 2000).

It is clear that food components must, by definition, be bioavailable in some form to exert biological effects. There have been major advances in the past few years in our knowledge regarding polyphenol absorption and metabolism (Scalbert et al., 2002; Walle, 2004). It is generally accepted that the bioavailability of phenolics is rather low and the values of the relative urinary excretion of the intake range from 0.3% for anthocyanins to 43% for isoflavones such as daidzin (Manach et al., 2005b). This demonstrates the great variability in the bioavailability of the different polyphenols. This bioavailability can be even lower when the food polyphenols have a large molecular weight, as is the case of hydrolyzable and condensed tannins and complex flavonoid conjugates with several sugars and acylated with hydroxycinnamic acids. The content of these complex phenolics in food is generally higher than that of simpler phenolics, and these complex molecules have been underestimated in many papers mainly due to analytical problems. The microbiota metabolites of these complex polyphenols are smaller molecules in which some of the original phenolic hydroxyls have been removed, and these metabolites are generally better absorbed in the intestine (Selma et al., 2009). This indicates that the systemic effects of polyphenols can be modulated by the microbial metabolism. The hydrolysis of glycosides results in metabolites that are potentially more biologically active than the parent compounds (Selma et al., 2009). It has been shown that the glucoside isoflavones are very poorly absorbed in the small intestine compared with their aglycones because of their greater molecular weight and higher hydrophilicity. Furthermore, the glucosides are known to be less bioactive than their respective aglycones (Mariusz et al., 1999).

ANTIOXIDANT ACTIVITY AND FOOD

The antioxidant activity in foods is associated with the presence of polyphenols and vitamins. Although the HPLC methods used in the assessment of polyphenols and vitamins in foods are reliable, reproducible, and sensitive, HPLC-MS methods are also required by highest sensitivity, whereas others techniques as spectrophotometric methods, GC, differential pulse voltammetry and the biosensor approach are less used (Romani et al., 2000). Several methods have been described to analyze antioxidant capacities, TEAC (Trolox Equivalent Antioxidant Capacity), FRAP (Ferric Reducing Ability of Plasma), TRAP (total radicaltrapping antioxidant parameter), and ORAC (Oxygen Radical Absorbance Capacity), being the ORAC method the most common (Zulueta et al., 2009; Chen et al., 2010). The ORAC method consists of measuring the decrease in the fluorescence of a protein as a result of the loss of its conformation

Table 2 The antioxidant activity in foods is associated with the presence of polyphenols and vitamins

Foods	Polyphenol	Vitamin A	Vitamin C	Vitamin E	References
Vinager	+				Qiu et al. (2010)
Blackberry	+				Sariburun et al. (2010)
Caper	+	+	+	+	Tlili et al. (2010)
Winter cherry	+		+		Laczkó-Zold et al. (2009)
Aloe vera	+	+	+	+	Oszoy et al. (2009)
Rose grape juice	+		+		Landete et al. (2007)
Wild rice	+				Qiu et al. (2009)
Tomatoes	+	+	+		Periago et al. (2008)
Potatoes	+		+		Leo et al. (2008)
Pistachio nut	+		+	+	Gentile et al. (2007)
Red wine	+				Fogliano et al. (1999)
Kei-apple juice	+		+		Loost et al. (2006)
Orange	+		+		Proteggente et al. (2003)
Onion	+		+		Yang et al. (2004)
Oils	+	+		+	Landete et al. (2008)
Fruit juice-skim milk	+	+	+		Zulueta et al. (2007)

when it suffers oxidative damage caused by a source of peroxyl radicals (ROO^-). The method measures the ability of the antioxidants in the sample to protect the protein from oxidative damage. The ORAC method has greater specificity and is capable of responding to a greater number of antioxidant compounds than the other methods (Zulueta et al., 2009; Chen et al., 2010).

As shown in Table 2, numerous publications have demonstrated the relation between antioxidant activity and content of polyphenols and vitamins in food. Nearly 90% of antioxidant activity in the human diet is obtained from fruits and vegetables. The polyphenols are the principal antioxidants found in food followed by the vitamin C and to lesser extent vitamin E and vitamin A (Scalbert et al., 2005b). Dietary intake of polyphenols is much higher than that of all other known dietary antioxidants, about 10 times higher than that of vitamin C and 100 times higher than those of vitamin E and vitamin A (Williamson and Holst, 2008).

Knowledge of the total antioxidant activities of foods is interesting and would be useful for epidemiologic purposes. In general, fruit and vegetables rich in anthocyanins (e.g., strawberry, raspberry, and red plum) demonstrated the highest antioxidant activities, followed by those rich in flavanones (e.g., orange and grapefruit), and flavonols (e.g., onion, leek, spinach, and green cabbage), while the hydroxycinnamate-rich fruit (e.g., apple, tomato, pear, and peach) consistently elicited the lower antioxidant activities (Proteggente et al., 2002).

To accomplish this, the total antioxidant activities in a variety of foods commonly consumed in Italy were analyzed by Pellegrini et al. (2003) using TEAC, FRAP, and TRAP assays. Among vegetables, spinach, peppers, and asparagus had the greatest antioxidant activities. Among fruits, the highest antioxidant activities were found in berries (i.e., blackberry, redcurrant, and raspberry). Among beverages, coffee, citrus juices, and wine had the greatest total antioxidant activities. Finally, of the oils, soybean oil had the highest antioxidant activity, followed by extra virgin olive oil, whereas peanut oil was less effective.

In general, berries had the greatest antioxidant capacity, with blackberry being the most effective. Its high antioxidant capacity is likely due to the high content of phenolic acids and flavonoids such as anthocyanins (Sariburun et al., 2010) (Table 2), which have demonstrated strong antioxidant activities in different model systems (Rice-Evans et al., 1995; Satué-Gracia et al., 1997). Citrus fruits exhibited intermediate antioxidant capacity, with oranges as the most effective followed by grapefruit. This result is in agreement with the higher concentrations of phenolic compounds and vitamin C present in orange with respect to grapefruit (Proteggente et al., 2003) (Table 2).

Among alcoholic beverages, red wines had the most antioxidant capacity followed by rose and white wines, in agreement with the literature (Fogliano et al., 1999). This is not surprising because phenolic compounds in wine derive mainly from the skin, seeds, and stems of grapes, making them important sources of the polyphenols that are transferred to the juice at the first stage of wine fermentation (Landete et al., 2007; Dani et al., 2009). Thus, the content of polyphenols is high in red wine in which the contact between juice and pomace is prolonged; it is intermediate in rose wine in which the contact is reduced compared with red wine and relatively low in white wine, which is usually made from the free-running juice without contact with the grape skins. Phenolic compounds, tocopherols, and carotenoids must be considered to assess the total antioxidant capacity of oils (Boskou, 1996; Landete et al., 2008). The contribution of polyphenols and vitamins in the antioxidant activity of vinegar (Qiu et al., 2010), caper (Tlili et al., 2010), winter cherry (Laczkó-Zold et al., 2009), aloe vera (Oszoy et al., 2009), wild rice (Qiu et al., 2009), tomatoes (Periago et al., 2008), potatoes (Leo et al., 2008), pistachio nut (Gentile et al., 2007), kei-apple juice (Loost et al., 2007), and onion (Yang et al., 2004) is also shown in Table 2.

The growing interest in new functional foods with special characteristics and health properties has led to the development of new beverages based on fruit juice-skimmed milk mixtures (Granato et al., 2010). The proliferation of ready-to-drink

beverages has caused the market to focus its interest on these products. Commercial conventionally pasteurized or sterilized beverages based on a mixture of fruit juice and skimmed milk were evaluated for their concentrations of vitamin C, vitamin A, and phenolic compounds and their total antioxidant capacity by Zulueta et al (2007) (Table 2). The antioxidant capacity (TEAC) of these beverages ranged from 3.60 to 0.61 mmol trolox/l. The main contribution to the total antioxidant activity was provided by vitamin C, followed by phenolic compounds. Lemons and oranges were the fruits associated with the greatest antioxidant capacity in the samples of fruit juice-skimmed milk mixtures analyzed by Zulueta et al. (2007).

Moreover, it is interesting to know how the content of vitamins and polyphenols and the antioxidant activity can be maintained or even improved through cultivar development, production practices, postharvest storage, and food processing. When the fruits are consumed fresh, antioxidant capacity is not lost due to any adverse effects of heat and oxidation during processing. Zulueta et al. (2007) observed as the antioxidant activity of lemon and orange was higher in the refrigerated samples than in the samples stored at room temperature. The antioxidant activity of lemon and orange is mainly due to vitamin C, when the fruit is stored at temperatures higher than 4°C the vitamin C concentration decreases. However, there is an increases in the antioxidant activity of strawberries and raspberries during storage at temperatures higher than 4°C, which is accompanied by increases in anthocyanins in strawberries and increases in anthocyanins and total phenolics in raspberries (Kalt et al., 1999). Although the vitamin C concentration decreases in strawberries and raspberries during storage, vitamin C has small contribution to the total antioxidant capacity of these fruits.

VITAMINS AND HEALTH

Vitamin A plays an important role in vision (Dingle and Lucy, 2008), bone growth, reproduction, cell division, and cell differentiation. Overall, the epidemiological evidence suggests that vitamin A and carotenoids, by their antioxidant properties, are important dietary factors for reducing the incidence of heart disease. Although there is considerable discrepancy in the results from studies in humans regarding this relationship, carefully controlled experimental studies continue to indicate that these compounds are effective for mitigating and defending against many forms of cardiovascular disease. More work, especially concerning the relevance of how tissue concentrations, rather than plasma levels, relate to the progression of tissue damage in heart disease is required (Palace et al., 1999) (Table 3).

Vitamin A is important for healthy bones (Ilich and Kerstetter, 2000) (Table 3). However, too much vitamin A has been

Table 3 Effects on the health associated to the intake of vitamins A, C, E and polyphenols

Antioxidant	Effect on health	References
Vitamin A	It is necessary for vision	Dingle and Lucy (2008)
	Reduces the incidence of heart disease	Palace et al. (1999)
	Healthy bones	Ilich and Kerstetter (2000)
	Improvement in the immune function	West et al. (1991)
	Improvement in the haematopoiesis	Kubota et al. (2007)
	Improvement in the skin health	Kafi et al. (2007)
	Nausea, jaundice, irritability, vomiting, blurry vision, headaches, hairloss,	Penniston and Tanumihardjo, (2006)
	Reduces muscle and abdominal pain and weakness	Yehya et al. (2009)
Vitamin C	Protects against cancers	Barry (2008)
	Protects from heart disease	Liu et al. (2008)
	Improvement of the health of cartilage, joints and skin	Wang et al. (2007)
	Maintaining a healthy immune system	Wintergerst et al. (2006)
	Improvement in the antibody production	Woo et al. (2010)
	Increase in the absorption of nutrients	Thankachan et al. (2008)
	Increases protection against H_2O_2-induced DNA strand breaks	Riso et al. (2010)
Vitamin E	Prevents coronary heart disease	Pryor (2000)
	Prevents the formation of blood clots	Traber et al. (2008)
	Decreases incidence of breast and prostate cancers	Weinstein et al. (2007)
	Brain protection	Muller et al. (2010)
	Reduces long-term risk of dementia	Devore et al. (2010)
	Decreases risk of Parkinson's disease	Miyake et al. (2010)
Polyphenols	Inhibit oxidation of LDL	Manach et al. (2005a)
	Inhibit platelet aggregation	Russo et al. (2001)
	Improve endothelial dysfunction	Schächinger et al. (2000)
	Lower risk of myocardial infarction	Corder et al. (2006)
	Effect anticarcinogenic	Yang et al. (2001)
	Prevent neurodegenerative diseases	Halliwell, (2001)
	Protect against neurotoxic drugs	Pan et al. (2003)
	Are used in the treatment of diabetes	Zunino et al. (2007)
	Are used in treatment to prevent osteoporosis	Atmaca et al. (2008)
	Inhibit non-heme iron absorption	Hurrell et al. (1999)

linked to bone loss and an increase in the risk of hip fracture (Melhus et al., 1998). Scientists believe that excessive amounts of vitamin A trigger an increase in osteoclasts, the cells that break down bone (Oreffo et al., 1988).

Retinol is the form of vitamin A that causes concern. In addition to getting retinol from their diets, some people may be using synthetic retinoid preparations that are chemically similar to vitamin A to treat acne, psoriasis, and other skin conditions. These preparations have been shown to have the same negative impact on bone health as dietary retinol (Biesalski, 1989). Use of these medications in children and teens also has been linked to delays in growth.

Vitamin A also plays a role in a variety of functions throughout the body, such as gene transcription (McGrane, 2007), immune function (West et al., 1991), embryonic development (Maden, 2000) and reproduction, hematopoiesis (Kubota et al., 2007), and skin health (Kafi et al., 2007) (Table 3).

Since vitamin A is fat-soluble, disposing of any excesses taken in through diet is much harder than with water-soluble vitamins B and C, thus vitamin A toxicity may result. This can lead to nausea, jaundice, irritability, vomiting, blurry vision, headaches, hairloss, muscle and abdominal pain and weakness, drowsiness and altered mental status (Penniston and Tanumihardjo, 2006; Yehya et al., 2009) (Table 3).

Vitamin C is an important antioxidant, helps protect against cancers (Barry, 2008), heart disease (Liu et al., 2002); it is part of the cellular chemistry that provides energy; it is essential for the production and the quality of sperm (Akmal et al., 2006), and for making the collagen protein involved in the building and health of cartilage, joints, skin, and blood vessels (Wang et al., 2007; Duarte et al., 2009) (Table 3). Vitamin C helps in maintaining a healthy immune system (Wintergerst et al., 2006); it is needed for antibody production (Woo et al., 2010) and acts to increase the absorption of nutrients (including iron) in the gut (Thankachan et al., 2008) (Table 3).

Cruciferous vegetables as broccoli contain compounds with antioxidant properties (carotenoids and vitamin C). So, broccoli intake was associated with increased protection against H_2O_2-induced DNA strand breaks and lower levels of oxidised DNA bases from smokers. This protective effect could be related to an overall improved antioxidant status by the content in antioxidant compounds as carotenoids and vitamin C (Riso et al., 2010). Moreover, several studies have found that vitamin C inhibits experimental hepatocarcinogenesis. However, other studies have observed that vitamin C does not affect or actually enhances hepatocarcinogenesis (Glauert et al., 2010).

Oxidative stress is associated with reduced ascorbate levels. The plasma ascorbate concentration in a patient with oxidative stress (measured as less than 45 μmol/L of ascorbate) is lower than that of a healthy individual (61.4–80 μmol/L of ascorbate). According to McGregor and Biesalski (2006), increasing the individual's plasma ascorbate level may have therapeutic effects in cases of oxidative stress ascorbate is particularly effective in protecting the vascular endothelium, which is especially vulnerable to oxidative stress. The restoration of ascorbate levels may have therapeutic effects in diseases involving oxidative stress. The rapid replenishment of ascorbate is of special clinical significance in critically ill patients who experience drastic reductions in ascorbate levels, which may be a causal factor in the development of circulatory shock. Supraphysiological levels of ascorbate, which can only be achieved by the parenteral and not by the oral administration of vitamin C, may facilitate the restoration of vascular function in the critically ill patient.

Carr et al. (2000) suggested that ascorbate (vitamin C) and -tocopherol may protect against atherosclerosis by several mechanisms. These mechanisms include inhibition of LDL oxidation and inhibition of leukocyte adhesion to the endothelium and vascular endothelial dysfunction. Overall, ascorbate appears to be more effective than -tocopherol in mitigating these pathophysiological processes, most likely as a result of its abilities to effectively scavenge a wide range of reactive oxygen and nitrogen species and to regenerate -tocopherol from its radical species. In contrast, -tocopherol can act either as an antioxidant or a pro-oxidant to inhibit or facilitate, respectively, lipid peroxidation in LDL. However, this pro-oxidant activity of -tocopherol is prevented by ascorbate acting as a coantioxidant. Therefore, an optimum vitamin C intake or body status may help protect against atherosclerosis and its clinical sequelae, whereas vitamin E may only be effective in combination with vitamin C (Carr et al., 2000).

Many claims have been made about vitamin E's potential to promote health and prevent and treat disease. The mechanisms by which vitamin E might provide this protection include its function as an antioxidant and its roles in anti-inflammatory processes, inhibition of platelet aggregation, and immune enhancement. Evidence that vitamin E could help prevent or delay coronary heart disease comes from several sources (Pryor, 2000) (Table 3). In vitro studies have found that the nutrient inhibits oxidation of low-density lipoprotein (LDL) cholesterol, thought to be a crucial initiating step for atherosclerosis. Vitamin E might also help prevent the formation of blood clots that could lead to a heart attack or venous thromboembolism (Traber et al., 2008) (Table 3).

Antioxidant nutrients like vitamin E protect cell constituents from the damaging effects of free radicals that, if unchecked, might contribute to cancer development (Lee et al., 2005). Vitamin E might also block the formation of carcinogenic nitrosamines formed in the stomach from nitrites in foods and protect against cancer by enhancing immune function (Chow and Hong 2002).

Some researches link higher intakes of vitamin E with a decreased incidence of breast and prostate cancers. Weinstein et al. (2007) observed α-tocopherol supplementation (50 mg daily for 5–8 years) reduced prostate cancer incidence by 32%.

Brain has a high oxygen consumption rate and abundant polyunsaturated fatty acids in the neuronal cell membranes. Researchers hypothesize that if cumulative free-radical damage to neurons over time contributes to cognitive decline and neurodegenerative diseases, such as Alzheimer's disease, then ingestion of sufficient or supplemental antioxidants, such as vitamin E,

might provide protection (Muller, 2010). Higher intake of foods rich in vitamin E may modestly reduce long-term risk of dementia (Devore et al., 2010) and higher intake of vitamin E and β-carotene may be associated with a decreased risk of Parkinson's disease (Miyake et al., 2010) (Table 3).

POLYPHENOL AND HEALTH

Polyphenols can inhibit oxidation of LDL in vitro; this type of oxidation is considered to be a key mechanism in atherosclerosis (Manach et al., 2005a) (Table 3). These antioxidants affect result in the decreased oxidation of LDL lipids and of α-tocopherol (Zhu et al., 1999). Polyphenols may exert antithrombotic effects. They inhibit platelet aggregation in vitro (Russo et al., 2001). They were also shown to inhibit platelet aggregation in several animal models: the consumption of red wine (rich in polyphenols), rather than white wine or alcohol, in rats prevented the platelet rebound effect (measured by ex-vivo thrombin-induced platelet aggregation), otherwise observed in the hours following alcohol withdrawal (Ruf et al., 1995). Polyphenols can improve endothelial dysfunction, an early event in atherogenesis. Endothelial dysfunction is associated with different risk factors for atherosclerosis before the plaque is formed; its use as a prognostic tool for coronary heart disease has been proposed (Schächinger et al., 2000). Associations between polyphenol intake or the consumption of polyphenol-rich foods were examined in several epidemiological studies. For example, both the consumption of tea and a moderate consumption of wine have been regularly associated to a lower risk of myocardial infarction in both case-control and cohort studies (Corder et al., 2006), or catechin (Figure 4) intake has also been associated to a lower risk of coronary death but not to stroke (Arts et al., 2001).

Anticarcinogenic effects of polyphenols are also well documented in animals. Polyphenols, when given to rats or mice before and/or after the administration of a carcinogenic agent or the implantation of a human cancer cell line, are most often protective and induce a reduction of the number of tumors or of their growth (Yang et al., 2001) (Table 3). These effects have been observed at various sites, including mouth, stomach, duodenum, colon, liver, lung, mammary, or skin. Many polyphenols, such as quercetin, catechins, isoflavones, lignans, flavanones, ellagic acid, red wine polyphenols, resveratrol (Figure 4), or curcumin, were tested; all of them showed protective effects in some models. The anticarcinogenic properties of polyphenols could, thus, be explained by many different mechanisms. To explain their protective effect by their antioxidant properties and inhibition of DNA oxidative damage is certainly an oversimplification (Scalbert et al., 2005a). However, various antioxidants, including polyphenols, inhibit NF-kB activation, probably through triggering a redox-sensitive signal in the cells (Ahmad et al., 2000). The inhibition of such transcription factors by polyphenols may play an essential role in the prevention of cancers (Nomura et al., 2000). Beyond these, many hypotheses on mechanisms of action, the most difficult task, remain to demonstrate their anticarcinogenic effects in humans.

A clear distinction between cancer treatment at pharmacological doses and cancer prevention at dietary levels of exposure should be made when discussing experimental results obtained on animal models or on cell lines grown in vitro. The confusion is often maintained in purpose, to communicate on the beneficial health effects of polyphenol-containing food products. For example, resveratrol (Figure 4) has interesting anticarcinogenic properties that may lead to the development of new drugs (Athar et al., 2007). Its presence in wine and absence in any food sources has stimulated the interest of the industry to promote the health properties of wine. The question of doses is essential, as opposite effects have been observed at different exposure levels. Caffeic acid induces hyperplasia and tumors in the forestomach and kidney when administered in the diet of rats or mice at a dose of 0.5–2% of the diet, whereas it shows anticarcinogenic effects at doses of 0.05–0.15% (Lutz et al., 1997). The final evidence on the prevention of cancers by polyphenols will come from clinical and epidemiological studies. Tumor biomarkers are useful tools for prognosis, for the monitoring of therapy in various cancers, and for the evaluation of the influence of diet on the disease (Sturgeon 2002). Some polyphenols have been shown to reduce the levels of tumor biomarkers in different cancer cell lines. Genistein decreased the expression of protein-specific antigen in prostate cancer cells, epicatechin gallate, or genistein significantly reduced in a human lung cancer cell line, the levels of heterogeneous nuclear ribonucleoprotein B1, a new biomarker for early clinical diagnosis of lung cancer (Fujimoto et al., 2002). However, clinical evidence of an effect of polyphenols on tumor biomarkers is still very limited.

Neurodegenerative diseases as Alzheimer's disease and Parkinson's disease are dependent of oxidative stress, which particularly affects brain tissues (Halliwell, 2001), and antioxidants may, therefore, contribute to their prevention (Canturi-Castelvetri et al., 2000). Feeding aging rats a diet supplemented with aqueous extracts of spinach, strawberry, or blueberry rich in polyphenols improved their cognitive functions and neuronal signal transduction (Joseph et al., 2007). Blueberries rich in anthocyanins were particularly effective. These effects were not explained by a sparing of vitamins E and C in the brain (Martin et al., 2000); a direct implication of polyphenols as antioxidants is, therefore, suspected. Polyphenols also protect experimental animals against some neurotoxic drugs whose toxicity is linked to a stimulation of oxidative stress (Pan et al., 2003) (Table 3). Dietary supplementation with grape polyphenols reduced the neurodegenerative changes induced by chronic ethanol consumption, and improved the synaptic function measured on isolated synaptosomes (Sun et al., 1999).

Polyphenols contained in many plants may explain some of their therapeutic activity in the treatment of diabetes (Zunino et al., 2007) (Table 3). The acute or chronic administration of polyphenols to experimental animals influences glycemia. Caffeic acid and isoferulic acid, when administered intravenously to rats, reduce the fasting glycemia and attenuate the increase

of plasma glucose in an intravenous glucose tolerance test (Hsu et al., 2000; Liu et al, 2000). These effects were observed in a genetic model of insulin-dependent diabetes of rats or in streptozotocin-treated rats, but are less pronounced in normal rats. More interestingly, some hypoglycemic effects were also observed with polyphenols administered orally, shortly before consumption of the glucose source (Scalbert et al., 2005b).

Isoflavones with weak estrogen-like activity have attracted much attention as a possible alternative treatment to prevent osteoporosis (Atmaca et al., 2008; Ma et al., 2008) (Table 3). Their osteoprotective effects have been evaluated in mice or rats in which an estrogen deficiency has been induced by ovariectomy. The supplementation of the diet with genistein, daidzein (Figure 4), or their glycosides during several weeks prevents the loss of bone mineral density and trabecular volume caused by the ovariectomy (Nakajima et al., 2001; Ishimi et al., 2000). These effects were observed at daily doses of 10–50 mg/kg body weight. The highest doses also induced uterine hypertrophy, but the lowest protective doses did not affect the uterine weight (Picherit et al., 2000).

Although, the polyphenols usually have beneficial effects on health, some harmful effects have been described as consequence of their antinutrient properties. For example, most dietary polyphenols have catechol group in their structures and, thus form very stable chelates with ferric ions. This fundamental property explains the inhibition of non-heme iron absorption by polyphenols and polyphenol-containing beverages, such as coffee, wine, or tea, as shown in several clinical trials (Hurrell et al., 1999) (Table 3). As these effects involve direct chelation of iron by polyphenols in the gut, they are only observed when the source of polyphenols is ingested together with the source of iron. This is why it is often recommended for people at risk of developing iron deficiencies to drink tea and other polyphenol rich beverages between the meals rather than during the meals (Hurrell et al., 1999) (Table 3).

Epidemiological evidence indicates that polyphenols may be protective against chronic diseases, although discrepancies are observed between "in vivo" and "in vitro" experiments (Cherubini et al., 1999). Then "in vitro" results often do not match the findings in the "in vivo" studies (Lotito and Frei 2003). This could be explained by the low bioavailability of polyphenols as above mentioned (Scalbert and Williamson, 2000; Carbonaro et al., 2001; Manach et al., 2004). Moreover, the antioxidant activity can be modified when the polyphenols are metabolized by body's tissues or by the colonic microbiota (Cerdá et al., 2004). For example, daidzin can be transformed into equol, a molecule with higher antioxidant activity, by the intestinal microbiota (Yuan et al., 2007). Some studies indicate that intake of food rich in ellagitannins and ellagic acid (pomegranates, black raspberries, raspberries, strawberries, walnuts) may be protective against chronic diseases, although "in vitro" results often do not match the findings in the "in vivo" studies. This could be explained by the low bioavailability of the antioxidant ellagitannins and ellagic acid, moreover both polyphenols are metabolized to urolithins, which have been reported as a less potent antioxidant compared to the ellagitannins (Cerdá et al., 2004). On the other hand, urolithins could display estrogenic and/or antiestrogenic activity with health benefits.

ANTIOXIDANT SUPPLEMENTATION

Numerous studies have demonstrated a positive relation between a healthy diet, especially high intake of fruit and vegetables and health. Bazzano et al. (2002) examined the relation between fruit and vegetable intake and the risk of cardiovascular disease. They studied 9608 adults aged 25–74 years and showed an inverse association of fruit and vegetable intake with the risk of cardiovascular disease and all that cause mortality in the general US population. However, some controversies have been observed in studies using antioxidant supplementation. Previous research on animal and physiological models suggested that antioxidant supplements have beneficial effects that could prolong life. Some observational studies also suggested that antioxidant supplements could prolong life, whereas other observational studies have demonstrated neutral or harmful effects (Willett and Stampfer, 2001; Fletcher and Fairfield, 2002; Bjelakovic et al., 2004; Miller et al., 2005; Vivekananthan et al., 2003). The society needs evidence from randomized trials to decide if antioxidant supplements should be used for prevention.

Despite the absence of efficacy of antioxidant vitamins reported in larger randomized trials, two important articles have favored the universal use of multivitamins by consumers (Willett and Stampfer, 2001; Fletcher and Fairfield, 2002). The multivitamins recommended, however, contain vitamin A and vitamin E, two compounds that have not been proven to reduce cardiovascular morbidity or mortality, and may adversely affect lipid concentrations when used at higher doses. Willett and Stampfer (2001) believe that vitamin E supplements are reasonable for most middle-aged and older Americans who are at increased risk for coronary disease, even Fletcher and Fairfield (2002) suggested that physicians should make specific efforts to learn about their patients' use of vitamins to ensure that they are taking vitamins. However, Bjelakovic et al. (2009) did not find evidence to support antioxidant supplements, even they suggested that supplementation with vitamin A, β-carotene, and vitamin E may increase mortality. Previously, Bjelakovic et al. (2004) could not find evidence that antioxidant supplements can prevent gastrointestinal cancers; on the contrary, they seem to increase overall mortality and Miller et al. (2005) demonstrated as high-dosage of vitamin E supplements may increase the mortality. The lack of a salutary effect after administration of vitamin E in diverse populations was also observed by Vivekananthan et al. (2003).

A literature review about of supplementation of vitamins reveal that low levels of the antioxidant vitamins (vitamins A, E, and C) may increase risk for several chronic diseases, and in these cases, the controlled supplementation of vitamins is beneficial to health, the vitamin supplements should not exceed

the RDA. However, an intake of vitamins supplements higher that RDA, and not controlled, can produce harmful effects.

On the other hand, the excess of polyphenols in the dietary intake rarely produce harmful effects, although antinutrient properties have been described and must be considered. A review of the supplementation studies by Nardini et al. (2007) concluded that polyphenols supplementation, either as purified compounds or food extracts, showed some inhibitory effects on platelet aggregation, both in humans and in animal models. Although the extent of the inhibition varies in a wide range, depending on the experimental conditions used, epidemiological studies suggested that high polyphenols intake from diet is associated with reduced risk for cardiovascular diseases.

BIOMARKERS OF EXPOSURE FOR ANTIOXIDANT NUTRIENTS AND FOR OXIDATIVE STRESS

The studies "in vitro" help to know the effects of vitamins on health. However, controversies are observed between "in vitro" and "in vivo" studies Huang et al. (2002). Moreover, although the use of diet to estimate exposure to vitamins has clear advantages in terms of translating associations with chronic disease risk to nutrient recommendations and prudent dietary patterns, it is difficult to establish that dietary antioxidants or other nutrients are themselves causally related to the development or prevention of chronic diseases. By it, the use of biomarkers of exposure for antioxidant nutrients and biomarkers of oxidative stress status has been suggested (Mayne et al., 2003).

The levels of vitamin A can be measured in plasma or in serum using HPLC approaches (Craft, 1992). Vitamin A has also been measured in various tissues, especially adipose tissue (Parker, 1989), and studies have reported reasonable correlations between plasma and adipose tissue concentrations of vitamin A. The advantage of using adipose tissue as compared to plasma is that adipose tissue reflects longer-term exposure to lipid-soluble nutrients. Another tissue that has received increasing attention with regard to vitamin A concentrations is human skin. Vitamin A in skin has been measured using conventional HPLC methods (Peng et al., 1995), and newer methods such as reflection photometry (Stahl et al., 1998) and resonance Raman spectroscopy are also being proposed (Hata et al., 2000).

Epidemiologic studies of vitamin E and health often rely upon biochemical markers of exposure. Plasma concentrations of α-tocopherol in particular can be readily estimated using HPLC methods (Nierenberg et al., 1989). Adipose tissue obtained via needle biopsy can also be used to estimate exposure to vitamin E.

Plasma ascorbate can also be measured to estimate exposure to vitamin C; validated HPLC methods with documented performance over time are currently available (Margolis and Duewer, 1996). However, the use of plasma ascorbate to estimate exposure has several limitations in the context of epidemiologic research, plasma samples need to be specifically preserved at the time of sample collection to avoid degradation of the ascorbate and ascorbate levels in plasma fluctuate in response to current intakes, which makes fasting blood samples essential (Gibson, 1990).

The use of biomarkers of exposure for polyhenols is dependent on class of polyphenols intake. Moreover, the polyphenols are transformed by the body tissues and/or intestinal microbiota. So, equol and urolithins are biomarkers of the intake of isoflavones and ellagitannins, respectively. Peréz-Jimenéz et al. (2010) observed that polyphenols such as daidzein, genistein, glycitein, enterolactone, and hydroxytyrosol showed both a high recovery yield and a high correlation with the dose, which showed good sensitivity and robustness as biomarkers of intake throughout the different studies. Weaker recovery for anthocyanins and weaker correlations with dose for hesperidin, naringenin, epicatechin, epigallocatechin, quercetin, dihydrodaidzein, equol, and *O*-desmethylangolensin suggested that they are currently less suitable as biomarkers of intake.

Emphasis is now being placed on developing functional biomarkers of oxidative stress status (Mayne, 2003), that is, biomarkers that integrate the effect of exposure to oxidants coupled with the full range of antioxidant protective mechanisms in vivo (Mayne, 2003). Many such biomarkers are being studied including various measures of lipid, DNA, and protein oxidation. Some of these biomarkers are now being applied in epidemiologic research. The oxidative modification of LDL is thought to enhance atherogenicity. For this reason, the resistance of LDL to induced oxidative stress ex vivo has been used as a possible biomarker of oxidative defence, at least in the LDL particle itself (Mayne, 2003).

Measurement of the concentrations of F2-isoprostanes, a series of prostaglandin, has proved to be valuable in assessing oxidative stress in vivo. Montuschi et al. (1998) showed that the level of oxidative stress is enhanced in patients with interstitial lung diseases as reflected by increased concentrations of 8-epi-prostaglandin F2 alpha in bronchoalveolar lavage. Kadiiska et al. (2005) concluded that measurements of malondialdehyde and isoprostanes in plasma and urine are potential candidates for general biomarkers of oxidative stress. Also, Mangal et al. (2009) demonstrated that the analysis of 7,8-dihydro-8-oxo-2'-deoxyguanosine in plasma is a biomarker of oxidative stress in cellular DNA.

Dalle-Donne et al. (2003) observed relationships among high level of protein–protein carbonyl groups, oxidative stress and diseases such as Alzheimer's disease, rheumatoid arthritis, diabetes, sepsis, chronic renal failure, and respiratory distress syndrome. Then, the protein carbonyl groups could be used as biomarkers of oxidative stress. Also, transcription factor NF-kB is used as a potential biomarker for oxidative stress Van den Berg et al. (2001).

CONCLUSIONS

Endogenous defence mechanisms are inadequate for the complete prevention of oxidative damage, and different sources

of dietary antioxidant such as vitamin A, C, and E and polyphenols may be especially important by their antioxidant properties. Fruits and vegetables are the main sources of antioxidants. Current evidence strongly supports a contribution of polyphenols and vitamins to the prevention of cardiovascular diseases, cancer, and osteoporosis and suggests a role in the prevention of neurodegenerative diseases and diabetes mellitus.

Much of the evidence on the beneficial effects of dietary polyphenols is derived from experiments performed in vitro or in animal models, and by using concentrations much higher than those generally contained in the human diet. Moreover, often the compounds tested were polyphenol aglycones or their sugar conjugates rather than their active metabolites.

Significant progress has been made in the field of cardiovascular diseases in human, and today it is well established that a healthy diet, especially high intake of fruit and vegetables, do improve health status, as indicated by several biomarkers closely associated with cardiovascular risk. Epidemiological studies tend to confirm the protective effects of polyphenols and vitamins consumption against cardiovascular diseases. In contrast, evidence for protective effects of polyphenols and vitamins against cancers, neurodegenerative diseases, and brain function deterioration is still largely derived from animal experiments and in vitro studies. It is clear, that polyphenols and vitamins clearly improve the status of different oxidative stress biomarkers and help improve our health. Then, dietary intake of natural antioxidants is an improved aspect of the body's defence mechanism.

Identification of new food components with antioxidant effects in biological systems would, therefore, be helpful in designing dietary strategies to maximize the in vivo antioxidant potential in humans.

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