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Dietary Derived Antioxidants: Implications on Health

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1. Introduction

Oxidative stress state is involved in the aging process as well as in a vast array of pathological conditions, including atherosclerosis, cardiovascular complications, diabetes, cancer, and neuropsychiatric and neurodegenerative diseases. Oxidative stress is characterized by an imbalance in the cellular redox state in favour of a high formation of reactive oxygen species (ROS), overcoming the reducing capacity of the human antioxidant defence system, which has the role to eliminate excess ROS production, avoiding the oxidative action of such species on cellular components (nucleic acids, lipids, proteins or carbohydrates) and thereby their resulting adverse effects.

In general, oxidative stress can result from a high production of ROS or a poor antioxidant defence system, which is in part depending on exogenous molecules which could act as antioxidants, such as vitamin C, vitamin E, carotenoids and polyphenols. ROS at low or moderate concentrations in human tissues are required for optimum cellular functioning, owing to their crucial role in many physiological functions, such as stimulating cellular signaling, gene expression, the regulation of immune responses and fostering antioxidant defense mechanisms (Valko et al., 2007; Bouayed & Bohn, 2010). While the double-edged effects of ROS are well known, with toxic and deleterious effects at high concentrations, the biphasic effects of antioxidants have been postulated recently (reviewed by Bouayed & Bohn, 2010). Interaction of antioxidants with ROS present at physiological concentrations required for optimal cell functioning could disrupt the balance between oxidant production and antioxidant protection, being believed to be critical in maintaining healthy biological systems. This has been earlier stressed in transgenic animals overexpressing antioxidant enzyme systems (e.g., superoxide dismutase (SOD) and glutathione peroxidase (GPx)) (Mirochnitchenko et al., 1995; Kondo et al., 1997; Bouayed & Bohn, 2010). Exogenous antioxidants at high concentrations could also behave as prooxidants or by activating other cellular responses that could result in detrimental effects such as inflammatory reactions

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(Bouayed & Bohn, 2010). However, exogenous antioxidants at nutritional doses, as occurring in their natural matrices such as in fruits and vegetables, are necessary to complete the scavenging action of the endogenous antioxidant defense system. Indeed, several laboratory, epidemiological, and intervention studies have suggested that antioxidants from fruits and vegetables can act as chemopreventive agents against several diseases related to oxidative stress, and are of interest especially in the prevention of chronic diseases (reviewed by Bouayed & Bohn, 2010). The use of antioxidants (e.g. inhibitors of xanthine oxidase) as therapeutic agents is also emerging, e.g. to treat hypertension (reviewed by Fang et al., 2009). However, the health-promoting effects of vitamin C, vitamin E, carotenoids and polyphenols may also occur independently from their antioxidant properties, such as by interacting with cellular signalling pathways, interacting with e.g. inflammatory processes or cell differentiation (reviewed by Bouayed & Bohn, 2010).

In this chapter, important classes of antioxidants occurring in our diet are presented. The necessity of exogenous antioxidants to maintain optimal health and prevent chronic diseases is discussed. The health-promoting effects of antioxidants within fruits and vegetables are also emphasized. Changes occurring during and following ingestion and digestion of bioactive compounds prior to reaching target organs and exerting their activity are also briefly reviewed.

2. ROS and antioxidant defence system

2.1 ROS

ROS are constantly generated during normal and aberrant cell metabolism, which relies on the use of molecular oxygen. Mitochondria constitute the principal cellular site producing ROS, as the majority of intracellular oxygen (*ca.* 85%) is consumed in these organelles. During mitochondrial respiration, high amounts of energy required for our organism are constantly extracted from organic molecules resulting finally in complete reduction of oxygen by 4 electrons leading to water and carbon dioxide formation. However, during oxidative phosphorylation, 1-3% of electrons leak prematurely from the respiratory complexes I and III of the mitochondrial electron transport chain, forming the superoxide free radical anion ($O_2^{\bullet-}$), resulting from monoelectronic reduction of oxygen (Delattre et al., 2005; Valko et al., 2007). The superoxide anion ($O_2^{\bullet-}$) is also generated, e.g. enzymatically by xanthine oxidase, known for its physiologic role in purine metabolism, NAD(P)H oxidase, especially during the oxidative burst stimulated by phagocytosis in immune cells and cytochromes P450 involved in metabolism I phase.

$O_2^{\bullet-}$ is considered to be the main precursor of ROS such as hydrogen peroxide (H_2O_2), hydroxyl radicals (OH^{\bullet}), alkoxyl radicals (RO^{\bullet}), and peroxyradicals (ROO^{\bullet}), among others (reviewed by Bouayed, 2010). Their order of reactivity has been determined as follows: $O_2^{\bullet-} < ROO^{\bullet} < OH^{\bullet}$. Thus, the anion superoxyde radical ($O_2^{\bullet-}$) has a low reactivity, contrary to the hydroxyl radical (OH^{\bullet}), which has a high reactivity, making it a very dangerous radical with a very short half-life *in vivo* (Delattre et al., 2005). Indeed, when OH^{\bullet} radicals are produced *in vivo*, they react close to their site of formation, explaining the non-selectivity of OH^{\bullet} radicals toward cellular components. Other reactive species including ozone (O_3), peroxy nitrite anions ($ONOO^-$), nitrogen dioxide radicals ($^{\bullet}NO_2$) and hypochlorous acid ($HOCl$) could react with biomolecules without preference or specificity. Peroxyl radicals

(ROO•) present an intermediate reactive species with respect to $O_2^{\bullet-}$ and OH^{\bullet} radicals; consequently ROO• may be more rapidly eliminated by antioxidants than $O_2^{\bullet-}$. The negative electric charge of $O_2^{\bullet-}$ impedes its diffusion across membranes, also limiting its range of action. However, its protonated form (hydroperoxyl radical, HO_2^{\bullet}), although constituting only *ca.* 0.3% of all superoxide radicals present in the cytosol of cells, is more reactive than its precursor ($O_2^{\bullet-}$), and also possesses the ability to cross cellular membranes (Delattre et al., 2005; Valko et al., 2007; Franco et al., 2009).

Despite being less reactive, the toxicity of $O_2^{\bullet-}$ is mainly attributed to its capacity to generate highly reactive species such as OH^{\bullet} via the Haber-Weiss reaction, or also $ONOO^-$, which are non-radical oxidizing molecules able e.g. to cause DNA fragmentation and lipid oxidation (Fig. 1) (Delattre et al., 2005; Valko et al., 2007). $ONOO^-$ is the result from the reaction of $O_2^{\bullet-}$ with nitric oxide ($\bullet NO$), a nitrogen-centered radical and an important cellular messenger molecule, and thus the product is considered both as an oxidant (ROS), and a nitrating agent (reactive nitrogen species, RNS). The protonated form of $ONOO^-$ (peroxynitrous acid, $ONOOH$), which could be easily formed at physiological pH, can decompose into OH^{\bullet} and $\bullet NO_2$, another RNS. However, it seems that the formation of nitrosoperoxycarbonate ($ONOOCO_2^-$) is more plausible *in-vivo*, following the reaction of $ONOO^-$ with CO_2 , due to

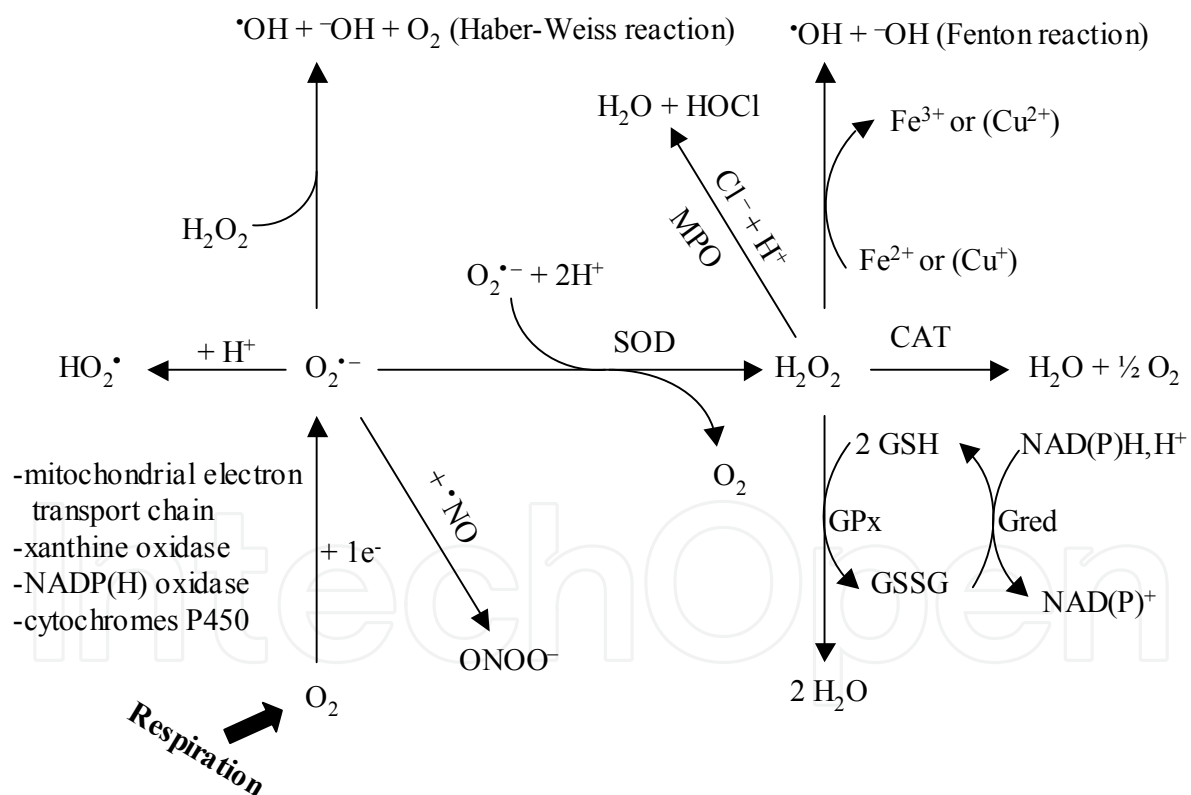


Fig. 1. Principal cellular pathways producing and metabolizing ROS. SOD, CAT, GPx, Gred and MPO mean superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase and myeloperoxidase, respectively. The reaction with MPO is specific for phagocytic cells. Fenton reaction could also involve other transition metals. GSSG and GSH stand for oxidized and reduced glutathione, respectively. NAD(P)⁺ and NAD(P)H stand for oxidized and reduced nicotinamide adenine dinucleotide phosphate, respectively.

the abundance of CO_2 following respiration. The decomposition of ONOOCO_2^- results in the formation of $\cdot\text{NO}_2$ and carbonate radical ($\text{CO}_3^{\cdot-}$), a ROS (Halliwell, 2006). For the above reason of multiple possibilities for interaction between nitrogen and oxygen containing reactive species, many authors usually use the collective term reactive oxygen and nitrogen species (RONS) to include both ROS and RNS. The major component of intracellular ROS *in vivo* is considered H_2O_2 , formed by its precursor $\text{O}_2^{\cdot-}$. Albeit being of non-radical nature, H_2O_2 is more reactive than $\text{O}_2^{\cdot-}$, having the ability to freely pass across cell membranes, and to generate more reactive molecules such as $\text{OH}\cdot$ via e.g. the Fenton reaction, or HOCl in phagocytic cells involving phagocyte-derived myeloperoxidase (MPO) (Fig. 1) (Splettstoesser & Schuff-Werner, 2002; Halliwell, 2006). Due to its microbicidal activity, HOCl (and OCl^-) contributes to the destruction of internalized bacteria and fungi by phagocytes (Halliwell, 2006).

2.2 Endogenous antioxidants

Cells are equipped with systems allowing for scavenging these oxidative species. This detoxifying system or antioxidant defense system is encompassing enzymatic and non-enzymatic antioxidants, with the latter based on endogenous (e.g. glutathione and coenzyme Q) as well as exogenous reducers (e.g. vitamin C and polyphenols) that are predominantly derived by dietary intake (table 1). In terms of enzymatic antioxidant

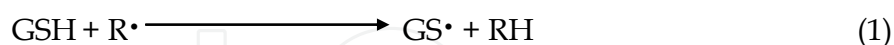
Antioxidant defense system	
Endogenous antioxidants	Exogenous antioxidants
<p>Enzymatic antioxidants</p> <ul style="list-style-type: none"> - Superoxide dismutase (SOD): enzyme detoxifying superoxide radical ($\text{O}_2^{\cdot-}$) - Catalase (CAT) and glutathione peroxidase (GPx): enzymes involved in the detoxification of peroxides (CAT against H_2O_2, and GPx against both H_2O_2 and ROOH) - Glutathione reductase: enzyme involved in the regeneration of glutathione - Thioredoxin reductase: enzyme involved in the protection against protein oxidation - Glucose-6-phosphate dehydrogenase: enzyme involved in the regeneration of NADPH <p>Non-enzymatic antioxidants (principal intracellular reducing agents) Glutathione (GSH), uric acid, lipoic acid, NADPH, coenzyme Q, albumin, bilirubin</p>	<p>Principal dietary antioxidants from fruits, vegetables and grains</p> <ul style="list-style-type: none"> - Vitamins: vitamin C, vitamin E - Trace elements : zinc, selenium - Carotenoids: β-carotene, lycopene, lutein, zeaxanthin - Phenolic acids: chlorogenic acids, gallic acid, caffeic acid, etc - Flavonols: quercetin*, kaempferol*, myricetin* - Flavanols: proanthocyanidins and catechins - Anthocyanidins: cyanidin* and pelargonidin* - Isoflavones: genistein*, daidzein* and glycitein* - Flavanones: naringenin*, eriodictyol* and hesperetin* - Flavones: luteolin* and apigenin*

* and their glucosides

Table 1. Human antioxidant defense systems include endogenous (enzymatic and non-enzymatic) and exogenous antioxidants, with the diet being the main exogenous source (Bouayed & Bohn, 2010)

defense systems, superoxide dismutase (GPx), glutathione peroxidase (GPx) and catalase (CAT) are the most known and prevalent antioxidant enzymes aiming to sequentially reduce $O_2^{\bullet-}$ and H_2O_2 , avoiding the formation of oxidative species such as hydroxyl radicals ($\bullet OH$). For example, transgenic mice studies have shown the importance of antioxidative enzymes for optimal health, even for survival. Homozygous mutant mice lacking manganese superoxide dismutase (Mn-SOD) died within the first 10 days of life (Storey, 2004). Mice lacking the enzyme glutathione peroxidase-1 (GPx-1), which among other functions protects the lens of the eye against H_2O_2 -mediated oxidative damage, have developed central cataracts (Wang et al., 2009). Homozygous catalase (CAT) knockout mice, although apparently developing normally, have shown differential sensitivity to oxidant tissue injury in comparison to wild-type mice (Ho et al., 2004).

SOD catalyses the dismutation of superoxide radicals ($O_2^{\bullet-}$) into O_2 and hydrogen peroxide (H_2O_2), which is itself detoxified by either CAT or GPx to water. GPx detoxifying activity, which extends also to peroxides (ROOH), requires glutathione (GSH) as the electron donor, depending on glutathione reductase (Gred) that assures the regeneration of GSH from the oxidized form (GSSG) (see Fig. 1). Glutathione transferase (GST) plays a role in the detoxification of prooxidant xenobiotics, as well as peroxidised lipids by catalysing their conjugation with GSH, facilitating their excretion from the cell. GSH is the most prevalent endogenous, non-enzymatic antioxidant. GSH is considered as a major antioxidant in aerobic cells, functioning as an important cellular redox buffer antioxidant. GSH depletion has shown to cause systemic oxidative stress and other detrimental effects such as anxious behaviour in mice (Bouayed et al., 2009; Bouayed, 2011). Besides its role as substrate for GPx, GST and glyoxalase I, GSH can also directly scavenge free radicals by hydrogen donation, resulting in glutathyl radicals (GS^{\bullet}), following the reaction (1). However, other reactive thiyl radicals could be generated from GS^{\bullet} such as GSO^{\bullet} and $GSOO^{\bullet}$ (reactions (2-3)). In addition to GSH, cells contain other endogenous antioxidants including uric acid, lipoic acid, NADPH, coenzyme Q, albumin and bilirubin (table. 1). However, our antioxidant defense system requires exogenous antioxidants, e.g. vitamin C, vitamin E, polyphenols and carotenoids, to efficiently scavenge RONS acting interactively (e.g., additively or synergistically) in order to maintain or re-establish redox homeostasis.



2.3 Exogenous antioxidants

A compound can be defined as an antioxidant if it is able to either delay or prevent free radical-mediated oxidation (or autooxidation) of an oxidizable compound (e.g., DNA, proteins, lipids or carbohydrates), at low concentration compared to the substrate, generating a more stable radical (Halliwell, 1990; Rice-Evans et al., 1996). Several dietary compounds satisfy these two basic conditions of an antioxidant, including polyphenols and carotenoids, and some nutrients such as vitamin C or vitamin E, of which especially fruits, vegetables, and other plant foods such as whole grains, but also fish, meat, and dairy products constitute natural sources (table 2).

dietary antioxidants	rich dietary sources	concentration in foods (mg/100g)
vitamin C	bell pepper, citrus fruits	10-170
quercetin	apples, onions	4-46
carotenoids	leafy vegetables, plums, tomatoes, watermelon, carrots	0.2-10
EGCG	green tea	5-450#
selenium*	fish (dairy products, potato, rice)	1-150*
vitamin E	fish, meat, leafy vegetables	0.2-10
isoflavonoids	soy, beans, peanuts	0.1-155

* $\mu\text{g}/100\text{g}$; #mg/cup (ca. 225 mL of tea beverage)

Table 2. Examples of antioxidant concentrations in fruits and vegetables (Bouayed & Bohn, 2010)

2.3.1 Polyphenols

This group constitutes the majority of dietary antioxidants (and also of secondary plant metabolites). Plants typically produce polyphenols as a defence against herbivores and various stresses in general. It is estimated that in Westernized countries, polyphenol intake is approx. 0.4-1g/d and capita (reviewed by Bouayed and Bohn, 2010), with higher intake for persons following a vegetarian diet. Food sources that are especially rich in polyphenols include, among others, potato, plums, leafy vegetables, whole grain products, and coffee (Souci et al., 2000).

Several *in vitro* studies have shown that polyphenols are the major contributors with respect to the total antioxidant activity of the majority of fruits and vegetables. Over 8.000 polyphenolic molecules have been identified and can be classified into flavonoids and non-flavonoid phenolics. Certain authors consider (poly)phenols to be all secondary phytochemicals that have at least two phenol subunits. However, (poly)phenols are also defined as all secondary metabolites possessing an aromatic benzene ring that is substituted by at least two hydroxyl groups, including their functional derivatives (reviewed by Bouayed, 2010). Moreover, in the classification given by Manach et al. (2004), even phenolic acids bearing only one hydroxyl group on the aromatic ring and acrylic acids, such as coumaric acids, are included in the polyphenol definition.

Flavonoids have a common structure consisting of 2 aromatic rings that are linked together by 3 carbon atoms that form an oxygenated heterocycle. This large group, which constitutes the most prevalent in the human diet, is divided into 6 subgroups, including flavonols (e.g. quercetin), flavones (e.g. apigenin), isoflavones (e.g. daidzein), flavanones (e.g. hesperetin), anthocyanidins (e.g. cyanidin), and flavanols (catechins and proanthocyanidins). Non-flavonoid polyphenolics include phenolic acids (e.g. chlorogenic acid), lignans (e.g. secoisolariciresinol) and stilbenes (e.g. resveratrol) (Manach et al., 2004).

Polyphenols scavenge free radicals ($R\cdot$) possessing an unpaired electron either by donation of hydrogens or electrons, resulting in comparatively stable phenoxyl ($\text{PhO}\cdot$) radicals (neutral ($\text{PhO}\cdot$) or cationic ($\text{PhO}^{+\cdot}$) molecules, respectively), which are stabilized by

delocalization of unpaired electrons around the aromatic ring (Rice-Evans et al., 1996, Bouayed et al., 2011a and 2011b). However, from an energetic point of view, it has been debated that phenolics favour hydrogen atom transfer mechanisms, in which lower energies are involved (Leopoldini et al., 2011). The radicals derived from oxygen represent the most important class of radical species generated in living systems. However the term antioxidant is often used to describe the scavenging activity of all reactive radicals including e.g. RNS radicals. The potential scavenging abilities of phenolics mainly depend on the number and the position of hydrogen donating hydroxyl groups on the aromatic cycles of the phenolic molecules (Rice-Evans et al., 1996). For example, aglycones or polyphenols with 2 hydroxyl groups on aromatic residues are better free radical scavengers than their glycoside forms or polyphenols with a single hydroxyl group.

Depending on their structures, polyphenols (e.g. tea polyphenols) could also act by chelating prooxidant transition metal ions such as Fe^{2+} , which are involved in reactions eliciting free radical production, including hydroxyl radicals (OH^\bullet) and alkoxy radicals (RO^\bullet) (Dufresne & Farnworth, 2001). Polyphenols that are able to scavenge lipid peroxy (LOO^\bullet) and lipid alkoxy (LO^\bullet) radicals or act as singlet oxygen quenchers ($^1\text{O}_2$) are effective inhibitors of lipid peroxidation processes, owing to the recognized role of these reactive species to initiate or to propagate free radical lipid peroxidation in cell membranes. The polarity of polyphenols is variable, ranging from water-soluble polyphenols (e.g. catechins), to more poorly water-soluble (e.g. flavonoid aglycones such as quercetin), to lipophilic polyphenols (e.g. curcumin).

Many *in vitro* studies have clearly revealed the potent role of flavonoids in inhibiting lipid peroxidation and oxidation of low-density lipoproteins (LDL). It has been proposed that flavonoids near membrane surfaces are ideally located for scavenging free radicals generated in the aqueous phase. For example, it has been debated that catechins might prevent the oxidation of vitamin E (a lipophilic antioxidant) by scavenging hydrophilic radicals near membrane surfaces, whereas vitamin E scavenges lipid peroxy radicals (LOO^\bullet) as hydrogen donor to stop free radical chain reactions (chain-breaking antioxidant). Polyphenols could also play a role in the regeneration of vitamin E through reduction of its oxidized form (vitamin E $^\bullet$ radical) (Rice-Evans et al., 1996; Rice evens, 2001), acting synergistically. In some cases, polyphenols could exert their antioxidant activity by inhibiting the catalytic activity of many enzymes eliciting ROS formation, including xanthine oxidase, lipoxygenase, cyclooxygenase and NAD(P)H oxidase (Atmani et al., 2009).

In food matrices, bioactivity of polyphenols like all dietary antioxidants in the human body, depends firstly on their bioaccessibility (i.e. the release from the food matrix) and bioavailability (i.e. absorbable fraction that can be used for specific physiological functions in organs). Polyphenols of comparatively high bioavailability include isoflavonoids (absorption cover > 50%, Bohn, 2010), while e.g. anthocyanins are of very low bioavailability, usually ca. 1.7% (Sakakibara et al., 2009). The prerequisite for bioavailability of any compound is its bioaccessibility in the gut. Following their ingestion, native polyphenols may undergo several modifications in the gastrointestinal (GI) tract until absorption, changes that may also affect their antioxidant capacity (Bouayed et al., 2011b; 2011c). This process may concern especially polyphenols of high molecular weight such as tannins or polyphenols not absorbed in the small intestine (e.g. polyphenols linked to a rhamnose moiety) – which could be extensively metabolized by the microflora of the colon. In addition, the majority of polyphenols in nature occur as glycosides or esters, which require typically cleavage prior to the absorption, such as

by intestinal and microflora enzymes, especially cytosolic β -glucosidase, brush border inherent lactase phlorizin hydrolase or esterases.

However, cellular uptake of aglycones has been suggested to occur in their native form by passive diffusion. Absorbed polyphenols can directly undergo phase II metabolism as phenolic structures are generally unfavorable substrates to the cytochrome P450s (phase I metabolism). At nutritional doses, almost all polyphenols are conjugated to form *O*-glucuronides, sulfate esters and *O*-methyl ethers, by glucuronidation, sulfation and methylation, in the gut mucosa and later in the liver or kidney. Glucuronidation and sulfation of polyphenols may facilitate their rapid urinary and biliary excretion by increasing their hydrophilicity, and also may limit their potential toxicity. Bioaccessible unabsorbed polyphenols may play a role in the protection of the GI tract against RONS prior to their fecal excretion. In contrast to native polyphenols, less data exists on the antioxidant activity of bioavailable polyphenol phase II metabolites (conjugated derivatives). Despite the variable and overall relatively poor bioavailability of polyphenols (concentrations range between high nanomolar and low micromolar in human plasma and organs), polyphenols have been reported to be more efficient than vitamin C, vitamin E and carotenoids (concentration ranges between high micromolar and low millimolar in human plasma and organs) against oxidative stress at tissue levels (Scalbert et al., 2002; Manach et al., 2004; Yang et al., 2008; Pandey & Rizvi, 2009; Bouayed & Bohn, 2010; Bouayed et al., 2011b, 2011c).

2.3.2 Carotenoids

These tetraterpenoid (C-40) compounds are also naturally occurring substances with antioxidant potential, and found especially in colored fruits and vegetables but also eggs, algae, some seafood, and are synthesized by plants, bacteria and several fungi. So far, over 700 carotenoids have been identified, of which however only 40-50 species play a role in the human diet (reviewed by Bohn, 2008). It is estimated that approx. 9-16 mg carotenoids per day are consumed in industrialized countries (O'Neill et al. 2001). Food items rich in carotenoids include for example spinach (11 mg/100 g edible portion), tomatoes (5 mg/100 g), and carrots (20 mg/100 g) (Biehler et al. 2011).

Some carotenoids are considered as nutrients, such as alpha-, beta-, and gamma-carotene, and alpha- and beta-cryptoxanthin, exhibiting vitamin A activity following their metabolism into retinol by humans (Biehler & Bohn, 2010; Biehler et al., 2010). Carotenoids are pigments with several conjugated double bonds (polyene chain), which could be divided into oxygen containing carotenoids (oxocarotenoids or xanthophylls), and non-oxygen containing carotenoids (carotenes). Despite not showing vitamin A activity, lutein and zeaxanthin possess the ability to stabilize membrane integrity, and can efficiently act as secondary antioxidants by absorbing damaging blue light that enters the eye (Johnson, 2002; Maci, 2010), important e.g. for the prevention of age-related macular degeneration (Maci, 2010). These blue-light filtering phytochemicals are found especially in dark green leafy vegetables such as spinach, broccoli and kale. However, the main mechanism of antioxidant activity of carotenoids is radical scavenging and also quenching excited triplet states of oxygen (1O_2). Carotenoids (CAR-H) neutralize reactive radicals via electron

transfer, generating carotenoid radical cations (CAR-H^{•+}), which are less reactive due to the ability of their conjugated double-bonded structure to delocalize unpaired electrons. However, some carotenoids such as lycopene interacting with O₂^{•-} may yield the carotenoid radical anion (lycopene^{•-} + O₂). Carotenoids (CAR-H) could also scavenge free radicals (e.g. ROO[•]) by hydrogen atom mechanism transfer, resulting in alkyl radicals (CAR[•]). The potential scavenging effect of carotenoids is depending mostly on the length of the electron rich conjugated double bond system. This system can be as short as 3 double bonds in the case of phytoene, and as long as 11 conjugated double bonds in the case of lycopene, both two predominant carotenoids in tomato products. It has been also proposed that interaction of carotenoids (CAR-H) with some radicals (e.g. ROO[•]) could also occur by radical addition reaction, resulting in adduct formation (e.g. ROO-CAR-H[•]). It has been believed that carotenoids may combine with ROO[•] to form a large resonance stabilized radical (Palace et al., 1999; Mortensen et al., 2001; Krinsky & Yeum, 2003). It has been suggested that carotenoids have the potential to prevent a number of degenerative diseases including cancer, atherosclerosis and age-related macular degeneration via prevention of lipid peroxidation (Mortensen et al., 2001), see also following chapters. Carotenoids are hydrophobic compounds and thereby act as lipophilic antioxidants preventing polyunsaturated fatty acids from oxidative damages. In fact, carotenoids are incorporated into lipid membranes and thus could act as chain-breaking antioxidants by stopping free radical chain reactions (propagation of lipid peroxidation), scavenging lipid peroxy radicals (LOO[•]), avoiding the abstraction of allylic hydrogens from neighboring lipids. Inactivation of lipoxygenase activity by carotenoids is also proposed as another mechanism of protection against oxidative stress. Although it is still controversial, it has been debated that vitamin E regenerates the radical form of carotenoids and vice versa (Palace et al., 1999; Mortensen et al., 2001; Splettstoesser & Schuff-Werner, 2002; Krinsky & Yeum, 2003).

It is generally admitted that carotenoids are lipid-soluble antioxidants; however we can find exceptions of this rule with e.g. crocin, which is a water-soluble carotenoid. Differences exist also between the xanthophylls and the carotenes – while the latter typically rests rather deep in the apolar cores of lipid membranes, whereas the more polar oxocarotenoids interact more with the surface of lipid bilayers (Borel et al., 1996). The beneficial role of carotenoid consumption including the antioxidant effect of carotenoids has been questioned owing to previous findings of several studies including results from the CARET and the Finnish ATBC study, where comparatively high, isolated doses (supplements) of β-carotene resulted in increased lung cancer incidence in smokers. In fact, the general low absorption (ca. 5-20% in most cases, Bohn, 2008), has resulted in the idea of administering high doses in rather isolated form, such as in dietary supplements. The negative effects observed following the administration of supplements over prolonged periods of time however have never been related to regular dietary carotenoid consumption in healthy subjects. In contrast, several epidemiological studies have suggested that when consumed within fruits and vegetable, several beneficial effects can be attributed to these compounds, including reduced incidence of cancer, cardiovascular disease, and perhaps even osteoporosis (reviewed by Bouayed and Bohn, 2010; Bub et al., 2000). It can be hypothesized that safety and benefits of antioxidants rely mainly on their concentration, generally physiologic (nutritional) in their natural matrices such as within fruits and vegetables, which may explain the advantageous effects

of phytochemicals and nutrients in plant foods, acting additively and synergistically when consumed in a complex mixture (Bouayed and Bohn, 2010). In contrast to polyphenols, carotenoids appear to be less extensively metabolized, and are mainly excreted via bile and pancreas into the feces, or broken down into shorter apo-carotenals (Khachik et al., 2002a; 2002b; 2006) and further hydroxylated, and later possibly also excreted via the urine (Bohn, 2008).

2.3.3 Vitamin C and vitamin E

Vitamin C (ascorbic acid) is a water-soluble antioxidant, constituting one among the most prevalent dietary antioxidants found in fruits, vegetables and beverages. Dietary intake is usually in the area of 100 mg/d, with a DRI-RDA of 75mg/d (men) and 60mg/d (women) (National Academy of Sciences, 2000). Food items rich in vitamin C include bell peppers (ca. 120 mg/100g) and citrus fruits such as oranges (ca. 50 mg/100g) (Souci, 2000). Vitamin C contribution to the total antioxidant activity conferred e.g. by fruits was estimated to be generally less than 15%, except for kiwi fruits and honeydew melons (Wang et al., 1996), as typically, polyphenol content is up to one magnitude higher, and the antioxidant potential as measured by several tests is about comparable (per mass) to polyphenols. Ascorbic acid and its oxidized form, dehydroascorbic acid, both have vitamin C activity. Vitamin C is essential for the prevention of scurvy, due to its importance as a cofactor in the hydroxylation of proline to hydroxyproline, essential for the structure of collagen and other tissues (Shils et al., 2006). Several advantageous effects of vitamin C on human health have been stressed, such as the relationship between high plasma vitamin C concentration and reduced gastric cancer risk found in EPIC study (Jenab et al., 2006). Besides the antioxidant activity of vitamin C, which may explain its protective role against gastric cancer risk, several other activities could play a role, such as its ability to modulate cell growth kinetics and its putative antimicrobial activity, for example against *Helicobacter pylori*, a bacteria responsible for chronic ulcer and even stomach cancer. However, in the above case-control study, it seems that inhibition of carcinogenic *N*-nitroso compound formation within the stomach is more plausible as the chemopreventive mechanism of action of vitamin C.

The relationship between dietary intake and plasma vitamin C is non-linear, with maximum plasma vitamin C saturation (ca. 80 $\mu\text{mol/l}$) being reached with dietary intakes >1000 mg/day (Levine et al., 1996). In elderly men, a high dietary intake of both vitamin C and vitamin E, and a higher plasma concentration of vitamin C and β -carotene were associated with a protection against vascular dementia and improved memory performances, respectively (Masaki et al., 2000; Perrig et al., 1997). It has been reported that vitamin C in plasma dose-dependently increases resistance to lipid peroxidation (reviewed by Flora, 2009). However, at elevated oral intake, vitamin C (e.g. 500 mg/day over 6 weeks) has displayed prooxidant effects by increasing oxidative lymphocyte DNA damage of 30 healthy volunteers (Podmore et al., 1998). Furthermore, high doses can negatively impact the intactness of the gastro-intestinal lining. In contrast, some studies on healthy human volunteers consuming fruits and vegetables rich in vitamin C decreased levels of oxidative DNA damage (reviewed by Halliwell, 2002). In humans, vitamin C is predominantly present in form of ascorbate anions, and its oxidation sequentially leads first to monodehydroascorbate (by loss of an electron) and then dehydroascorbate (by loss of

hydrogen), which are relatively stable radicals, and the reaction therefore is reversible (reviewed by André et al., 2010; Flora, 2009). The ascorbyl radical is comparatively stable due to the stabilization of the adjacent vinyl group, transmitting electrons between the hydroxyl and the carbonyl (Flora, 2009).

Vitamin C can be transported into the cell either as its reduced form or dehydroascorbate (oxidized form), using active sodium-dependent transporters (SVCT1 and SVCT2) and facilitative glucose transporters (GLUTs) (André et al., 2010). GLUTs also permit the permeation of vitamin C into mitochondria. Besides the protective role of vitamin C against oxidative injury within the cytosol, this water-soluble nutrient can also confer protection to mitochondria that are targets of oxidative attacks resulting from ROS produced as a side product of the respiratory chain that is active within mitochondria. Several beneficial functions have been attributed to vitamin C, e.g. as regulative factors that may influence gene expression, apoptosis and other cellular functions, and playing a role as a cofactor for several enzymatic steps in the synthesis of monoamines, amino acids, peptide hormones, and carnitine (Santos et al., 2009).

Besides its implication in many biological processes, vitamin C is a powerful reducing agent, participating in several antioxidant mechanisms (Santos et al., 2009) by directly scavenging radicals, mediating electron transfer to ascorbate-dependent peroxidases or regenerating membrane bound vitamin E that has been oxidized, e.g. by lipid peroxyl radicals (LOO[•]), and thus indirectly limiting lipid peroxidation in cell membranes. Radical stabilization of the oxidized form of vitamin E (VE[•]) is conferred by electron delocalization around the aromatic ring of vitamin E, which is a phenolic antioxidant. The dietary recommended intake of vitamin E (DRI-RDA) is 12 mg/d (National Academy of Sciences, 2000), and main dietary sources include vegetable oils up to 200-300 mg/kg, and to a lesser extent, leafy vegetables and wholegrain foods (Souci, 2000). It has been considered that vitamin E is the major membrane bound antioxidant employed in humans, and thus this lipophilic chain breaking antioxidant has the ability to inhibit lipid peroxidation. Synergistic actions between vitamin C and vitamin E therefore appear important in their preventive activity against lipid peroxidation. Human trials and *in-vitro* studies have shown that oxidative stress causes a rapid depletion of vitamin C and vitamin E (reviewed by Bouayed & Bohn, 2010). As mentioned above, regeneration of vitamin E may also occur by intervention of other antioxidants such as glutathione dependent enzymes (GSH).

Eight different isomeric forms of vitamin E (4 tocopherols and 4 tocotrienols) have been found in nature. Tocotrienols (α , β , γ and δ) are identical in structure to tocopherols except for the degree of saturation in their side chain. However, α -tocopherol is considered to be the most active form of vitamin E in humans. It has been found that the concentrations of vitamin E isomers in human feces are higher than in plasma – possibly due to its limited absorption from the diet, suggesting that it could play a protective role against RONS produced in the GI tract (Halliwell et al., 2005). Although all vitamin E constituents can be absorbed from the GI tract, α -tocopherol represents the predominant form existing in human plasma with approx. 17 $\mu\text{mol/l}$, followed by γ -tocopherol at 1 $\mu\text{mol/l}$ (Halliwell et al., 2005). It has been estimated that prior to degradation, one molecule of α -tocopherol can deactivate up to 120 ¹O₂ molecules by resonance energy transfer (reviewed by André et al.,

2010). Thus, the main antioxidant function of vitamin E is the protection of biological membranes against oxidative damage of lipids either by quenching $^1\text{O}_2$ or by intercepting directly free radical intermediates (e.g. OH^\bullet , lipid radicals (L^\bullet), LO^\bullet , LOO^\bullet) by hydrogen donation generated during lipid oxidation, terminating this chain reaction of peroxidation. Following their lipophilicity, it is more plausible that vitamin E and β -carotene cooperate to protect membranes and lipoproteins from oxidative damages. Of course, as all antioxidants, vitamin E exerts other biological functions that are independent from its antioxidant properties, including modulation of cellular signaling, gene expression, immune response, and many more. However, as opposed to other vitamins, lack of vitamin E results in rather unspecific symptoms, also highlighting that this vitamin is mainly needed for its antioxidant activity *in vivo*. For example, deficiency of vitamin E has shown to provoke oxidative stress disturbances in transgenic rats. In another study, vitamin E deficiency in the murine brain caused brain oxidative stress and anxious behaviour (reviewed by Bouayed et al., 2009; Bouayed & Bohn, 2010, Bouayed, 2011).

3. Antioxidants and disease prevention: Potential mechanisms of action

3.1 RONS and chronic diseases

When oxidative injury of cellular bio-components is not repaired by the cellular repair mechanisms, constituting another defense system against oxidative damage, oxidative stress can lead to several dysfunctions that would result in development and progression of several human diseases including cardiovascular diseases (CVD), neurological diseases and cancer, and also to the acceleration of the aging process.

DNA, proteins and lipids represent the major targets of the oxidative action of RONS. For example, the causative link between peroxidation of lipids and lipoproteins, and several multifactorial diseases including CVD and cancer has been stressed in several reports (Halliwell, 2000; Atmani et al., 2009; Gupta et al., 2009; Rice-Evans, 2001). Lipid peroxidation and protein oxidation play also a role in the progression of Alzheimer's disease (Sultana et al., 2006). For many diseases, endothelial changes of the blood vessels do play a role. Peroxidation of circulating low-density lipoproteins (LDL) and especially within blood vessel walls is thought to be a possible initiator of the pathogenesis of atherosclerosis (Halliwell, 2000). RONS promote adhesion of platelets and monocytes to the endothelium, resulting in endothelial lesions, and eventually thrombosis and atherogenesis (Guo & Bruno, 2011).

In addition, lipid peroxidation in liver cells could, over prolonged periods of time, lead to liver diseases and diabetes (Atmani et al., 2009). Peroxides formed during lipid peroxidation processes can decompose into a vast array of toxic carbonyl products such as malondialdehyde (MDA), playing among others a role in the carcinogenesis process by interacting with cellular DNA, yielding e.g. DNA-MDA adducts that appear to be promutagenic (Gupta et al., 2009). The adverse effects of RONS are also involved in different stages of carcinogenesis by causing structural DNA damage, interacting with oncogenes, tumor suppressor genes or immunological mechanisms (Gupta et al., 2009). In this respect, the mitochondrial DNA (mtDNA) is also a target of oxidative injury, which could lead to lethal cell injury following mitochondrial genomic instability (Franco et al., 2009).

Cumulative DNA damage over time, especially in mtDNA, plays an important role in the aging process as well as in the pathogenesis of several acute and chronic neurodegenerative diseases including ischemic brain injury (Fiskum, 2000; Silva et al., 2008). In addition, at the level of mitochondria, lipid peroxidation induces the opening of the mitochondrial permeability transition pores (MPTP), resulting in the loss of the mitochondrial membrane potential (MMP), and subsequent impairments such as ATP synthesis, activating the intrinsic pathway of apoptosis, and playing a significant role in neurodegeneration following neurotrauma such as in ischemic and chronic disease-related neurodegeneration (Fiskum, 2000, Franco et al., 2009).

Oxidative stress could also play a key role in the pathogenesis of hypertension, counteracting the vasodilator effect of $\bullet\text{NO}$ in the vascular endothelium by favouring the formation of peroxynitrite (ONOO^-). It has been hypothesized that a high production of $\text{O}_2^{\bullet-}$, by e.g. xanthine oxidase in the vascular endothelium leads to the rapid formation of ONOO^- , as the reaction between $\text{O}_2^{\bullet-}$ and $\bullet\text{NO}$ is six-fold faster than the dismutation of $\text{O}_2^{\bullet-}$ by SOD. In addition, the non-availability of $\bullet\text{NO}$ would stimulate the release of the vasoconstrictor endothelin-1, and in turn, increases $\text{O}_2^{\bullet-}$ production by activating NADPH oxidase. As a result, the lack of $\bullet\text{NO}$ in the vascular system could result in hypertension. Endothelial vasodilator dysfunction is related to several diseases including atherosclerosis, coronary artery disease, ischemia, stroke, etc. (reviews: Fang et al., 2009; Guo & Bruno, 2011). On the other hand, due to oxygen-free radicals produced during normal cell respiration, molecular and cellular oxidative damages accumulate over time, and were hypothesized to result in aging, and ultimately death (free radical theory of aging, Harman, 1956).

3.2 Focus cancer

The advantageous effects of antioxidant properties of food ingredients (phytochemicals and nutrients) on human health occur owing to their ability to inhibit (or retard) lipid peroxidation (see chapter 2.2) and oxidation of other sensitive cellular bio-components, including DNA and proteins. Several *in vitro* studies have shown antimutagenicity and anticarcinogenicity effects of antioxidants (e.g. tea polyphenols including catechins) at different levels of cancer development, namely initiation, promotion and progression, albeit these properties could also be independent from the antioxidant mechanisms. Besides the direct protective effects of antioxidants against lipid peroxidation and DNA oxidation, resulting in the prevention against mutations and DNA strand breakage, antioxidants (e.g. epigallocatechin gallate (EGCG)) have the ability to inhibit the activation of procarcinogens by phase I enzymes and also to induce detoxification of active carcinogens by phase II enzymes, facilitating their excretion following their conjugation (Dufresne & Farnworth, 2001). Interestingly, rosmarinic acid, a dietary polyphenol, has exhibited another mechanism of protection against oxidative DNA damages *in vitro*, by enhancing DNA repair resulting from strand break formation (Silva et al., 2008).

Despite the promising *in vitro* chemopreventive effects of antioxidants, human supplementation trials with individual antioxidants have generally failed to prevent CVD and cancer formation or progression, even leading to controversial results, except in the

Linxian trial, in which the combined effect of β -carotene, vitamin E and various minerals (Zn, Se) in a poorly nourished population in China has yielded beneficial effects on the incidence on cancer in general (reviewed by Bouayed & Bohn, 2010). In contrast, earlier retrospective epidemiological studies have suggested preventive effects of colored fruits and vegetables rich in carotenoids, high β -carotene plasma concentrations against cancer risk, especially lung cancer. Epidemiologists have also presented fruits and vegetables rich in polyphenols including e.g. apples, onion and white grapefruit as protective strategies against lung cancer (reviewed by Bouayed & Bohn, 2010). Although it is thought that anticarcinogenicity of these food plant items was related to the entire effects of all ingredients of fruits and vegetables (e.g. vitamins, polyphenols, carotenoids, dietary fiber and many more) acting additively and synergistically, and unfolding several protective mechanisms; many researchers have aimed to attribute the advantageous effects of these plant foods to few or even individual components, such as β -carotene and quercetin, owing to their antioxidant properties including the chemopreventive activity of quercetin against carcinogens *in vitro* (reviewed by Bouayed & Bohn, 2010). Nevertheless, due to the many confounding factors, it is generally extremely difficult to attribute the observed beneficial health effects to specific ingredients. Moreover, it cannot be excluded that the so far targeted phytochemicals, including carotenoids and polyphenols, are merely indicators for a fruit and vegetable rich diet, or that they are indicative of additional, yet unidentified beneficial health compounds.

Thus, although a high intake of fruits and vegetables is believed to be a good way to prevent against cancer and other chronic diseases, recent prospective epidemiological studies such as the EPIC study have shed some doubt at the strength of this relationship, at least for certain types of cancers such as lung, breast and prostate cancers (reviewed by Key, 2011). However, several case-control studies and few prospective cohort studies have shown an inverse relationship between high fruits and vegetables intake and the risk of several types of cancers including cancers of the oral cavity, pharynx, larynx, oesophagus and stomach (reviewed by Key, 2011). In addition, based on an observational study on Korean dietary habits, showing that "westernization" of diet (i.e. high intake of calories and fats and limited intake of plant foods) has led to a rapid increase of mortality due to several types of cancers including lung (by 53%), breast (by 37%), pancreas (by 63%), prostate (by 200%) and colon (by 75%) cancers within one decade (1990-1999). These cancers were less often fatal when plant-based diets were adopted, thus highlighting the preventive effect of plant foods against cancer development (Lee et al., 2004, review).

3.3 Focus CVD

In addition to cancer, the advantageous effects of antioxidants are also recognized in the prevention of several other human chronic diseases, such as coronary heart disease (CHD) and stroke. Prospective cohort studies showed that the inverse relationship between the potential of prevention of fruits and vegetables against the above diseases depended on the amount of edible portions consumed per day. The protection against coronary heart disease was generally established when fruits and vegetables were consumed at >4 servings/d for several years often >8 years. In a meta-analysis of eight independent cohort prospective studies, it has been shown that consumption of >5 servings/d of fruits and vegetables

caused a stronger reduction in stroke (ischaemic and haemorrhagic stroke) compared to 3–5 servings, the latter consumption reducing stroke incidence significantly compared to <3 servings/d. A recommended portion is somewhat vaguely defined as 80–100 g (reviewed by Bouayed & Bohn, 2010).

In the world, certain dietary regimens are assumed to be healthier, providing high amounts of nutrients (vitamins, minerals) and non-nutrients (dietary fiber, carotenoids, polyphenols, monounsaturated fatty acids, etc), preventing the development (or the progression) of several human chronic diseases at epidemic level in several populations. For example, traditional Mediterranean regimens are based on diversity and high intake of plant-based foods such as olive oil, cereals, legumes, nuts and vegetables and also other food items such as honey, eggs and fish. Thus, moderate energy intake and limited animal fat are the landmarks of this regimen.

Several benefits have been attributed to Mediterranean diets, among them their ability to reduce several forms of cancer, cardiovascular diseases and related mortality (Psaltopoulou et al., 2004; Scarmeas et al., 2006; Lairon, 2007; Mekki et al., 2010; Fung et al., 2010). In this respect, a Greek prospective study has shown a negative relationship between Mediterranean regimen and hypertension (Psaltopoulou et al., 2004), which is an important precursor of other diseases such as renal insufficiency, stroke and especially several cardiovascular complications including atherosclerosis, myocardial infarction, congestive heart failure, peripheral vascular disease and sudden cardiac death. It has also been verified prospectively that a Mediterranean diet could reduce the risk of Alzheimer's disease (Scarmeas et al., 2006). In addition, dietary intervention studies have shown that the adoption of a Mediterranean diet reduced several cardiovascular risk factors in subjects at risk (primary prevention), and/or reduced cardiovascular events/mortality in patients following a first cardiac event (secondary prevention) (Reviewed by Lairon, 2007). It has also been recommended that the Mediterranean diet could improve dyslipidemia and prevent against lipid peroxidation and inflammation in chronic renal failure patients (Mekki et al., 2010).

Vegetarian diets could also be a good example to review the health-promoting effects of plant food ingredients. Comparisons between vegetarians and non-vegetarians (omnivores) have shown that vegetarians have in general, lower risk of mortality from ischemic heart disease, hypertension, stroke, type 2 diabetes and certain cancers. Differences have also been noticed regarding body mass index, total serum LDL levels, and blood pressure. However, it seems that persons following a vegetarian regimen, especially vegans, possibly will need to include some fortified foods or supplements, providing e.g. vitamin D, vitamin B₁₂, ω -3 fatty acids, iron, calcium, zinc and iodine, to equilibrate their diet and to maintain optimal health (reviewed by Fang et al., 2009).

The use of antioxidants as antihypertensive agents in both preventive and therapeutic approaches is also emerging. The inhibition of vascular endothelial xanthine oxidase may result in antihypertensive effects favouring NO-induced vasorelaxation. It has been shown that i.v. injection of 4-amino-6-hydroxypyrazolo[3,4-*d*]pyrimidine, a synthetic xanthine oxidase inhibitor, reduced the blood pressure of hypertensive rats to 70% of the initial blood pressure (review: Fang et al., 2009). Several natural antioxidants, e.g. some polyphenols

have the ability to inhibit xanthine oxidase and could be beneficial in the prevention or treatment of hypertension. Vascular oxidative stress plays a crucial role in vascular endothelial dysfunction by leading to disequilibrium between vasodilation and vasoconstriction. Besides impaired vasorelaxation, vascular endothelial dysfunction may also be related to platelet aggregation and monocyte adhesion (Guo & Bruno, 2011). Quercetin, a well-known antioxidant polyphenol, is regarded as a vasoprotective agent following its abilities to act as reducing, vasodilatory, anti-platelet, and anti-atherogenic compound. In addition, *in vitro* human cell studies have shown that quercetin, at physiological concentrations (0.001-1 μ M), is also able to increase the availability of \bullet NO by increasing endothelial nitric oxide synthase (eNOS) mRNA expression. Human studies have shown that quercetin supplementation increased plasma \bullet NO and decreased endothelin-1 within 2 h of ingestion in healthy participants. Although quercetin supplementation did not lower the rate of oxidized LDL (a risk factor of CVD) in healthy normal-weight persons, quercetin diminished oxidized LDL in obese patients. Quercetin supplementation also decreased blood pressures (systolic and diastolic) in hypertensive patients (reviewed by Guo & Bruno, 2011). As quercetin is a common polyphenol in plant foods such as apple, onion, plum, etc, it could be suggested that plant foods rich in quercetin may be beneficial for decreasing the risk of CVD.

3.4 Other chronic diseases and conditions

It has also been reported in several epidemiological studies, that antioxidant intake in elderly populations protected against several diseases and age related complications, which are more specific for the nervous system impairment, including dementia, cognitive deficiency and Alzheimer's disease (Grundman & Delaney, 2002). The brain is the most vulnerable organ to oxidative stress, especially during age, when the antioxidative system is prone to decline. The brain structure, which is rich in lipids, is very prone to lipid peroxidation resulting e.g. in decreased membrane fluidity and damage in membrane proteins, inactivating receptors, enzymes and ion channels, becoming a threat for neuronal function and even overall brain activity. Lipid peroxidation can disrupt membrane integrity, leading to neuronal cell death. The brain's high oxygen consumption and its modest antioxidant defenses constitute further reasons for the sensitivity of this vital organ to oxidative stress. Several food items have shown to protect aged animals against brain oxidation, improving cognitive function, and diminishing age-related anxiety. For example, aged rats fed for 10 weeks with a standard diet supplemented with fresh apple fruits have presented significantly lower oxidative stress and anxiety than aged rats fed with the standard diet. Interestingly, brain antioxidant status of aged rats fed with apple enriched diet, as assessed by SOD activity, was not different from young animals, fed with the standard diet with or without apples. Aged rats fed for one year with a diet containing olive oil naturally rich in antioxidants have displayed low anxiety and brain oxidative stress compared to aged rats fed either with a diet containing olive oil naturally low in antioxidants or with maize oil. Long-term intake of honey has also prevented rats from the side effects of the aging process, including high anxiety and spatial memory deterioration (Bouayed, 2011). From several studies, it appears that "anti-aging foods" including antioxidants will not allow increasing the life-span of species; however, they may permit to

increase the quality of life by both retarding side effects related to the aging, and preventing (or retarding) diseases of the old age including Alzheimer's and Parkinson's diseases.

4. Conclusion

It has been estimated that healthy food choices, with regular physical activity and non smoking habits, can prevent over 80% of CHD, 70% of stroke, and 90% of type-2 diabetes (Willett, 2006). Epidemiological (retrospective and prospective) investigations, case-control studies and dietary intervention studies have strongly suggested or shown the importance of plant foods rich in antioxidants in the prevention against several chronic human diseases. It is well accepted that prevention is the most persistent, cost-effective strategy to deal with chronic diseases. Thus, natural foods rich in antioxidants could be employed as a strategy in the prevention of several chronic human diseases. Antioxidants in their natural matrices are generally assumed to be safe, and their concentration physiologic. Furthermore, it is thought that the advantageous effects of antioxidants in natural food sources are due to their additive and synergistic action. Among additional mechanisms independent from antioxidant properties, several antioxidative mechanisms are proposed as being responsible for maintaining optimal health and also preventing diseases. The protection against free radical-mediated lipid peroxidation, DNA and protein oxidation, and oxidative stress-related mitochondrial dysfunction constitutes the principal way of natural antioxidants for the prevention against several diseases including cancer, cardiovascular complications, neurodegenerative diseases and the side effects of aging. Other antioxidative protective mechanisms such as absorption of UV blue light by certain carotenoids could also play a role in prevention. Further prospective studies, both with whole food items and individual dietary constituents are warranted and needed.

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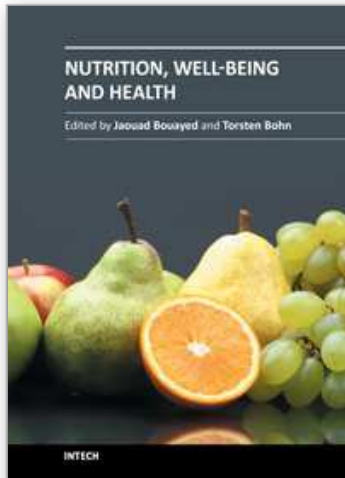
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In our modern society, expectations are high, also with respect to our daily diet. In addition to being merely "nutritious", i.e. supplying a variety of essential nutrients, including macro-nutrients such as proteins or micro-nutrients such as minerals and vitamins, it is almost expected that a good diet offers further advantages - especially well-being and health and the prevention of chronic diseases, which are, as we generally tend to grow older and older, becoming a burden to enjoying private life and to the entire society. These additional qualities are often sought in diets rich also in non-nutritive components, such as phytochemicals. In contrast to drugs, which are taken especially to cure or ameliorate diseases, it is expected that a healthy diet acts in particular on the side of prevention, allowing us to become old without feeling old. In the present book, rather than trying to give an exhaustive overview on nutritional aspects and their link to well-being and health, selected topics have been chosen, intended to address presently discussed key issues of nutrition for health, presenting a reasonable selection of the manifold topics around diet, well-being, and health: from the antioxidants polyphenols and carotenoids, aroma-active terpenoids, to calcium for bone health, back to traditional Chinese Medicine.

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