Compounds with Antioxidant Capacity as Potential Tools Against Several Oxidative Stress Related Disorders: Fact or Artifact?

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1. Introduction

Oxidative stress has been generating much recent interest primarily because of its accepted role as a major contributor to the aetiology of both normal senescence and severe pathologies with serious public health implications such as obesity, diabetes, atherosclerosis, metabolic syndrome, cancer etc. However, 'Living with the risk of oxidative stress is a price that aerobic organisms must pay for more efficient bioenergetics' (quoted from V. P. Skulachev).

The term oxidative stress is vaguely defined. In essence, it refers to a serious imbalance between production of reactive species and antioxidant defenses. Thus, oxidative stress can result from diminished levels of antioxidants but can also result from increased production of reactive species (Lushchak, 2011). The consequences of oxidative stress can include: firstly, adaptation of the cell or organism by upregulation of defence systems, which may first, completely protect against damage; second, protect against damage to some extent but not completely; or third, 'overprotect' (e.g. the cell is then resistant to higher levels of oxidative stress imposed subsequently). Secondly, cell injury, which involves damage (oxidative damage) to any or all molecular targets: lipids, DNA, proteins, carbohydrates, etc. Thirdly, cell death as the cell may first, recover from the oxidative damage by repairing it or replacing the damaged molecules, or second, it may survive with persistent oxidative damage or third, oxidative damage, especially to DNA, that may trigger cell death, by apoptosis or necrosis (reviewed by Perez-Matute et al., 2009). There are different types of

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reactive species: reactive oxygen species (ROS, thus, oxygen-containing molecules that are highly reactive), reactive chlorine species (RCN) and reactive nitrogen species (RNS). All these reactants contain free radicals as well as nonradicals. Low concentrations of these reactive species are necessary for normal cell redox status, cell function and intracellular signalling (Droge, 2002; Valko et al., 2007; Perez-Matute et al., 2009). However, in some disease states, free radicals are produced in excess and can damage DNA, proteins, carbohydrates and lipid constituents and compromise cell function leading to the development of type 2 diabetes, atherosclerosis, obesity, arthritis etc. Thus, it is clear that excessive production of free radicals causes damage to biological material and is an essential event in the aetiopathogenesis of various diseases. However, the question that has risen in the past years is whether uncontrolled formation of ROS is a primary cause or a downstream consequence of the pathological processes. In other words, it is still not clear what comes first, the chicken or the egg. However, what is clear is that there must be a balance between these reactive species and the antioxidants, whose main function is to counteract the deleterious effects of these reactive species. In fact, antioxidant is defined as any substance that when present at low concentrations compared with those of an oxidizable substrate, significantly delays or prevents oxidation of that substrate (Halliwell & Gutteridge, 1999). These defences include both enzymatic (superoxide dismutases, glutathione peroxidase, catalase, thioredoxin) and non-enzimatic systems (vitamins such as vitamin C, E, A, minerals such as selenium, zinc, cooper, bilirrubine, uric acid, some aminoacids etc).

Several studies have demonstrated an increased oxidative state (either caused by an increased ROS production or diminished levels of antioxidants) in serious pathologies such as obesity, cardiovascular diseases, metabolic syndrome, cancer etc. Thus, oxidative stress actually may be related with the mentioned processes. In this context, it is tempting to suggest that if oxidative damage significantly contributes to disease pathology, then, actions that decrease it (via decreasing ROS production or increasing endogenous levels of antioxidants) might be therapeutically beneficial. In fact, attenuation or complete suppression of oxidative stress as a way to improve several diseases has flourished as one of the main challenges of research in the last years. Thus, several approaches have been carried out in order to either decrease the high levels of ROS generated or boost the endogenous levels of antioxidants. Inhibition of ROS production through the development of inhibitors (natural or chemical) against the main sources of ROS generation offers an interesting approach. Thus, NADPH oxidase and mitochondria have been postulated as the main targets to reduce ROS production (reviewed by Pérez-Matute et al., 2009). Another strategy to decrease the consequences of an increased oxidative state is the investigation that is being carried out in the last years to prove the benefits from usage of antioxidant vitamins, minerals or drinks and foods with bioactive compounds to prevent these oxidative-stress-related diseases. Thus, this chapter will focus on the potential beneficial effects of modulating oxidative stress by several bioactive compounds with antioxidant properties.

2. Counteracting oxidative stress to improve health: Role of antioxidants

As previously mentioned, increasing amount of evidence suggests that oxidative stress is linked to pathophysiological mechanisms concerning multiple acute and chronic human

diseases (Dalle-Donne et al., 2006; Halliwell & Gutteridge, 2007). In this context, different strategies have been developed in order to counteract oxidative stress to improve health. We will focus on the modulation antioxidant status through a nutritional approach. Thus, and concerning the conventional antioxidant therapies that have been carried out in the last years, we can underline that there are two main ways to deal with this issue: to promote the ingestion of diets rich in several micro and macronutrients with antioxidant properties that could be beneficial for health (such as the well known Mediterranean diet) or to supplement the diet with specific bioactive compounds with antioxidant properties. In this sense, many diseases have been reported to benefit from antioxidant therapy and covering all of them in one chapter is not possible. However, it is important to note that those pathologies that may benefit the most from this antioxidant therapy are neurodegenerative diseases, Alzheimer disease, Parkinson disease, amyotrophic lateral sclerosis, cancer, stroke, obesity and diabetes (reviewed by Firuzi et al., 2011).

2.1 Diets with recognized benefits on oxidative stress and health: Diets rich in antioxidants

Epidemiological and experimental studies have demonstrated that plant-food intake decreases the risk of chronic diseases and therefore significantly contributes to the maintenance of health. For instance, the lower occurrence of cancer and cardiovascular diseases in the population around the Mediterranean basin has been linked to the dietary habits of this region. This so-called Mediterranean diet is essentially different from the diets consumed in Western and Northern European countries and is rich in nuts, fruits, vegetables, legumes, whole-wheat bread, fish, and olive oil, with moderate amounts of red wine, which is mainly consumed during meals. The components of this diet contain an ample source of molecules with antioxidant and anti-inflammatory actions, among which we can find omega-3 fatty acids, oleic acid, and phenolic compounds (Pauwels, 2011). There are several studies where the health benefits of consuming this diet have been demonstrated. Thus, the study of Dai et al. (2008) has demonstrated that the association between the Mediterranean diet and plasma oxidative stress is robust and is not confounded by genetic or shared environmental factors. Moreover, they demonstrated that a decreased oxidative stress is a plausible mechanism linking the Mediterranean diet ingestion to reduced cardiovascular disease risk (Dai et al., 2008). Moreover, it has been shown that subjects following a Mediterranean diet present low oxidised LDL levels, which seems to be one of the protective effects against cardiovascular events according to a PREDIMED (*Prevención Con Dieta Mediterránea*) cohort trial (Fito et al., 2007). Furthermore, the *French Paradox* is the observation that French people suffer a relatively low incidence of coronary heart diseases, despite having a diet relatively rich in saturated fats along with fruits, vegetables and red wine. In fact, this paradox has been attributed to the consumption of red wine and more specifically to polyphenols (antioxidants such as resveratrol) present in red wine. These effects underline the hypothesis that the Mediterranean diet may also neutralize the deleterious effects caused by the consumption of relatively high amounts of animal fats.

The dietary patterns based on the DASH (Dietary Approaches to Stop Hypertension) emphasizes the consumption of fruits, vegetables, and low-fat dairy products and the reduced ingestion of saturated fat, total fat, and cholesterol (as in the Mediterranean diet) as

it has been demonstrated that these patterns substantially lowered blood pressure and low-density lipoprotein cholesterol (Miller et al., 2006). Participants from the SU.VI.MAX (*Supplementation en Vitamines et Minéraux Antioxydants*) cohort who achieved the current daily fruit and vegetable intake recommendations within the DASH diet guidelines presented a lower increase in blood pressure with aging (Dauchet et al., 2007). In addition, a prospective study in the EPIC (European Prospective Investigation into Cancer and Nutrition) cohort evidenced that a high vegetables, legumes, and fruit diet was associated with a reduced risk of all-cause mortality, especially deaths due to cardiovascular disease underling the recommendation for the diabetic population to eat large amounts of vegetables, legumes, and fruit (Nothlings et al., 2008). Furthermore, fruit-enriched hypocaloric diets appear to be more effective against oxidative stress according to the study of Crujeiras et al. (2006). In fact, consumption of antioxidant substances contained in fruit could be a useful strategy in the design of hypocaloric diets that, with the weight reduction, could increase the improvement of cardiovascular risk factors related to obesity. Finally, in a case-control study, an inverse association has been found between the first acute myocardial infarction and the consumption of fruits among the Spanish Mediterranean diet (Martinez-Gonzalez et al., 2002).

Among all the foods included in these healthy diets (such as the Mediterranean diet), legumes have also been suggested to contribute to prevent cardiovascular disease and diabetes mellitus. Indeed, epidemiological studies have shown that Asian people consuming soy in their staple diet present much lower mortality and morbidity from cardiovascular disease than their counterparts in Western counties (Heneman et al., 2007). However, lentils, chickpeas, peas, and beans are the legumes more commonly consumed in Western countries but it has also been demonstrated that a non soybean legumes-based hypocaloric diet induced a higher decrease in blood lipids concentrations as well as lower lipid peroxidation markers related to obesity comorbidities as compared to a conventional and balanced hypocaloric diet (Crujeiras et al., 2007a).

All these studies mentioned above are examples that evidenced the beneficial effects of plant-food intake in promoting health and life-span in part attributed to their high level of antioxidant compounds, which contribute to decrease oxidative stress (Crujeiras et al., 2009). Some studies have also attributed antioxidative properties to fiber-enriched diets, since these compounds enhance the capacity to detoxify free radicals (Diniz et al., 2005). Fiber alters fat absorption from the diet by impairing lipid hydrolysis, resulting in increased fat excretion and as consequence, decreased lipid peroxidation probability. Moreover, fiber secondary metabolites that arise from bacterial fermentation in the colon may have antioxidant properties (Diniz et al., 2005). Reinforcing this idea, a significant correlation between antioxidant power in plasma and dietary fiber plus fructose evidenced the beneficial effects of fruit intake on antioxidant capacity in obese women (Crujeiras et al., 2006). In addition, the fruit (Crujeiras et al., 2006) or legumes (Crujeiras et al., 2007a) hypocholesterolemic effects were in parallel with oxidative stress improvement when evaluated by means of the prooxidant and antioxidant ratio in plasma (Crujeiras et al., 2006) or lipid peroxidation biomarkers (Crujeiras et al., 2007a), suggesting an indirect antioxidant effect of these plant-foods intake mediated by the hypocholesterolemic induction.

The antioxidant effect of plant-food could be also produced by the action of lesser known compounds or by the combination of different compounds occurring in the foods with direct or indirect antioxidant effects (Crujeiras et al., 2007b). In this context, fructose has been proposed to produce specific effects on oxidative stress. Animal models fed with a high content of fructose have shown a significant increase in antioxidant capacity and prevention of lipid peroxidation (Girard et al., 2005). This fruit monosaccharide stimulates uric acid synthesis due to its rapid metabolism by fructokinase (Heuckenkamp & Zollner, 1971). Uric acid has been widely recognized in the scientific literature as a metabolic compound with high antioxidant power participating as an *in vivo* scavenger (Glantzounis et al., 2005). Thus, it has been suggested that urate is responsible for the increase in antioxidant capacity after consuming apples as fruit in healthy subjects (Lotito & Frei, 2004) and after following a fruit-based hypocaloric diet in obese women (Crujeiras et al., 2006). However, the role of uric acid on oxidative stress and health is not clear enough and conflicting results have been provided in different studies, as will be discussed later on in the vitamins section. Taking together these observations, it is conceivable that besides of the direct effect of the antioxidant compounds of plant-foods present in the Mediterranean and other healthy diets, some reported antioxidant health effects can be also associated with the metabolic effect of these foods that indirectly reduces the oxidative damage probability in presence of free radicals. Thus and despite the fact that the Mediterranean diet along with other diets enriched in fruits, fiber or legumes are beneficial for health, it is very difficult to identify which component of the diet is responsible for the positive effects (in fact, in many cases is the association of several compounds). Thus and although the presence of antioxidants has been claimed by many to be responsible for the beneficial effect of vegetables and fruits, it has also been postulated that low content of fat in these foods may be the responsible cause (reviewed by Firuzi et al., 2011). Because of that, several investigations have been carried out to analyze the effects of specific compounds with antioxidant properties more than a food which contains plenty of compounds. In this sense, the most potent antioxidants with beneficial effects on health are presented in the following part of this chapter. It is important to note that we here present a brief review of the most important antioxidants found in foods more than in antioxidants that are currently in clinical use and that have been extensively reviewed elsewhere (Firuzi et al., 2011). Indeed, we have focused the chapter on a nutritional approach of oxidative stress related diseases more than on a pharmacological approach. However, a list with the main antioxidant drugs approved for clinical use is provided in table 1.

Antioxidant	Clinical Use
Edaravone	Ischemic stroke
Idebenone	Alzheimer disease (?)
N-Aceylcysteine	Acetaminophen overdose, mucolytic, dry eye syndrome
α-Lipoic acid*	Diabetic neuropathy
Micronized purified flavonoids fraction (MPFF, Daflon 500®)	Persistent venous ulcers
0-β-hydroxyethyl-rutosides (Venoruton®)	Chronic venous insufficiency
Silibinin (Leaglon®)	Hepatoprotective (?), chemopreventive
Baicalein and catechins (flavocoxid)	Osteoarthritis

*Lipoic acid, due to its dietary source will be deeply discussed in this chapter

Table 1. Antioxidant drugs approved for clinical use in various diseases (Firuzi et al., 2011).

2.2 Supplementation with specific bioactive compounds with antioxidant properties

2.2.1 Lipoic acid

α-Lipoic acid (LA), also known as 1,2-dithiolane-3-pentanoic acid or thioctic acid, is a promising dietary bioactive molecule because of its recognized therapeutic potential on several diseases such as diabetes, vascular disease, hypertension, alzheimer and inflammation (Shay et al., 2009; Firuzi et al., 2011). In fact, LA (dexlipotam) has been clinically approved and used for diabetic neuropathy as pointed out in table 1. In fact, it has been used in Germany for treatment of symptomatic diabetic neuropahty since several years ago.

The two enantiomers of this acid are the R form and the S form. Both R-LA and its reduced form, dihydrolipoic acid or 6,8-dimercaptooctanoic acid (DHLA) exert powerful antioxidant properties although DHLA seems to be more effective (Packer & Suzuki, 1993). Their antioxidant functions involve: quenching ROS (reactive oxygen species), regeneration of endogenous and exogenous antioxidants involving vitamin C, vitamin E and glutathione, chelation of redox metal including Cu(II) and Fe (II) and repair of oxidized proteins.

Lipoic Acid can be found in different foods such as spinach and cabbage, liver and meat, whole wheat and yeast of beer, but it is also endogenously produced by the liver through the lipoic acid synthase (LASY) machinery. Deficiency of LASY results in an overall disturbance in the antioxidant defence network, leading to increased inflammation, insulin resistance and mitochondrial dysfunction (Padmalayam et al., 2009).

Lipoic Acid is also an essential cofactor for mitochondrial bioenergetic enzymes (Smith et al., 2004). In fact, it is well known the intimate connection of LA with cell metabolism and redox state (Packer et al., 1997) as LA is essential for normal oxidative metabolism and plays a vital role as a cofactor in mitochondrial dehydrogenase reactions (Gilgun-Sherki et al., 2002).

Oxidative stress has been linked to different pathologies such as endothelial dysfunction. In this context, several studies noted that LA plays an important role in the activation of endothelial nitric oxide synthase (eNOS), which is one enzyme responsible for nitric oxide (NO) release/production, which, in turn, is an important regulator and mediator of numerous processes in the nervous, immune and cardiovascular systems. These actions include vascular smooth muscle relaxation resulting in arterial vasodilation and increasing blood flow (Federici et al., 2002; Montagnani et al., 2002). An *in vitro* study in human endothelial cells showed that treatment with LA potentate endothelial NO synthesis and bioactivity by mechanisms that appear to be independent of cellular GSH levels (Visioli et al., 2002). Furthermore, one trial demonstrated that the administration of LA improved vasodilation in patients with metabolic syndrome (Sola et al., 2005), corroborating its positive effects in endothelial dysfunction.

Recent studies also suggest that chronic oxidative stress plays an important role in the aetiology of human obesity (Vincent et al., 2007; Wang et al., 2011). Inadequacy of antioxidant defences probably begins with a low dietary intake of bioactive compounds with antioxidant capacity (Taylor et al., 2006). In fact, it has been demonstrated that obese individuals have a lower intake of bioactive compounds compared with non-obese persons. Based on that, different studies suggest a possible nutritional intervention with antioxidants eg. LA for treating obesity which has been associated with an increased oxidative state caused by either an increase in ROS production or a decrease in the antioxidant levels

(Prieto-Hontoria et al., 2009; Carbonelli et al., 2011; Koh et al., 2011). In this context, it has been demonstrated that LA reduces body weight and adiposity in rodents (Kim et al., 2004; Prieto-Hontoria et al., 2009) and humans (Carbonelli et al., 2011). Several mechanisms may contribute to the anti-obesity effects of LA including the suppression of hypothalamic AMPK (adenosine monophosphate-activated protein kinase) activity (Shen et al., 2005), which, in turn, leads to a reduction in food intake. Other mechanism that could also contribute to the anti-obesity effects of LA is the stimulation of energy expenditure by increasing Ucp-1 mRNA levels in brown adipose tissue (Kim et al., 2004). A very recent study has also demonstrated that LA increases energy expenditure by enhancing AMPK in skeletal muscle, a cellular energy sensor that can regulate peroxisome proliferator-activated receptor-gamma coactivator-1alpha (PGC-1alpha), which is a master regulator of mitochondrial biogenesis. Thus, this study demonstrated that LA improves skeletal muscle energy metabolism in aged mice possibly through enhancing AMPK-PGC-1alpha-mediated mitochondrial biogenesis and function (Wang et al., 2010). Furthermore, the inhibitory actions of LA on intestinal sugar transport could also contribute to a lower feed efficiency observed in LA-treated animals (Prieto-Hontoria et al., 2009). Another mechanism that could also contribute in reducing adiposity is the ability of LA to inhibit adipocyte differentiation, as described by Cho et al., (2003). These inhibitory effects of LA on adipocyte differentiation appear to be mediated by reduced levels of PPARγ and C/EBPα, as well as by the activation of MAPK. Another study suggests that the anorexigenic effect of LA are mediated by inhibition the activity of various liver enzymes involved in fatty acid synthesis and desaturation such as glucose 6 - phosphate dehydrogenase, malic enzyme, pyruvate kinase enzyme, ATP-citrate lyase and fatty acid synthase (Huong & Ide, 2008).

In addition, LA has also beneficial actions in both glucose and lipid metabolism and, it has been proposed, as mentioned before, as a potential therapy for insulin resistance and type 2 diabetes. LA positively interacts with the insulin pathway and glucose handling in muscle and adipocytes, by modulating the IR/PI3K/Akt pathway and GLUT4 translocation (Shay et al., 2009). LA also promotes mitochondrial biogenesis in adipocytes and muscle through a stimulation of PGC-1α, contributing to improve the defective mitochondrial function associated to diabetes/obesity (Shen et al., 2008a; Shen et al., 2008b). Furthermore, a very recent study has demonstrated that LA treatment over a period of 2 months improves fasting blood glucose (FBG), insulin resistance (IR), and glutathione peroxidase (GH-Px) activity in type 2 diabetes (T2DM) patients (Ansar et al., 2011).

Furthremore, LA treatment in rats with thioacetamide-induced liver fibrosis, inhibited the development of liver cirrhosis, as indicated by reductions in cirrhosis incidence, hepatic fibrosis, and AST/ALT activities (Foo et al., 2011). Several studies from our group have also demonstrated the beneficial effects of LA supplementation on fatty liver in a diet-induced obesity rat model (Valdecantos et al., 2010b, 2011a,b).

Finally, several trials have also suggested the potential use of LA in cancer therapy (Novotny et al., 2008) due to its ability to induce apoptosis in cancer cells (Shi et al., 2008; Choi et al., 2009). However, the molecular mechanisms underlying the anti-carcinogenic actions of LA are not well understood.

To sum up, LA seems to be a promising candidate against not only diabetes (in fact is one antioxidant approved for clinical use in diabetic neuropathy) but also against obesity and its

comorbidities (glucose and lipid impairments) as well as against cardiovascular events, some cancers and liver injuries.

2.2.2 Polyphenolic compunds: Resveratrol

Grapes (*Vitis vinifera L.*) contain high concentrations of polyphenols, especially flavonoids. The amount and composition of biologically active compounds presented in grapes and grape products vary greatly according to the species, variety, maturity, seasonal conditions, production area and yield of the fruit. The main grape polyphenols are anthocyanins in red grapes and flavan-3-ols in the case of white grapes. Red grapes contain more total polyphenols than white grapes. Grape seeds and skins are also an important dietary source of flavonoids, and seeds contain significant amounts of proanthocyanidins or condensed tannins. The most common commercial product derived from grapes is wine, a moderately alcoholic drink made by fermentation of juice extracted from fresh, ripe grapes. Its moderate consumption is suggested in the Mediterranean diet as cited before. The processing of grapes to yield wine transforms the polyphenols present in grapes and as a result the main polyphenols in wine are flavan-3-ols, flavan-3,4-diols, anthocyanins and anthocyanidins, flavonols, flavones, condensed tannins and a characteristic biologically active compound, resveratrol – a stilbene whose concentration can range from 1 5 to 3 mg/l (reviewed by Perez-Jimenez & Saura-Calixto, 2008). Resveratrol (trans-3,5,4'-trihydroxystilbene) is also found in various plants, including berries and peanuts. Moreover, this compound is now available in tablets on the market as a dietary supplement (not for clinical use).

A remarkable range of biological functions have been ascribed to this molecule. For example, resveratrol has shown cardioprotective actions (Hung et al., 2000), anti-cancer effects (Vanamala et al.) and anti-inflammatory and antioxidant properties (de la Lastra & Villegas, 2007). Its cardiovascular properties, including inhibition of platelet aggregation and promotion of vasodilation by enhancing the production of nitric oxide, have also been described (Cucciolla et al., 2007). It has also been reported to have many biological activities and protect against several neurodegenerative disorders such as Alzheimer's disease (Sun et al., 2010), but also to protect against oxidative stress in liver as well as steatosis in obese rats (Sebai et al., 2010; Gomez-Zorita et al., 2011) and against other diseases including AIDS (James, 2006; Zhang et al., 2009; Touzet & Philips, 2010), age-related illnesses and, more recently, obesity (Macarulla et al., 2009; Alberdi et al., 2011; Lasa et al., 2011). In fact, it seems to mimic the effects of energy restriction, thus leading to reduced body fat and improved insulin sensitivity. The mechanisms underlying these positive effects on obesity include: inhibition of preadipocyte proliferation and adipogenic differentiation, stimulation of basal and insulin-stimulated glucose uptake and inhibition of *de novo* lipogenesis (Fischer-Posovszky et al.). Resveratrol may also influence the secretion and plasma concentrations of some adipokines such as adiponectin and TNF-α and inhibits leptin secretion from rat adipocytes (Baur et al., 2006; Szkudelska et al., 2009). Resveratrol also regulates lipolysis via adipose triglyceride lipase (Lasa et al., 2011).

Several studies have suggested that activation of SIRT1 and AMPK plays a key role in the metabolic effects of resveratrol (Feige et al., 2008; Um et al., 2010). Sirtuins may provide novel targets for treating some diseases associated with oxidative stress. More specifically, SIRT1 has been shown to regulate metabolism and stress response by acting on several transcription factors and cofactors, histones and other chromatin proteins and components

of DNA repair machinery. A recent research has also shown that resveratrol modulates tumor cell proliferation and protein translation via SIRT1-dependent AMPK activation (Lin et al.). In this context, resveratrol has been proposed as a potential dietary compound against various cancers including breast and colon tumors. Resveratrol may affect all three discrete stages of carcinogenesis (initiation, promotion, and progression) by modulating signal transduction pathways that control cell division and growth, apoptosis, inflammation, angiogenesis, and metastasis (Bishayee, 2009). Recently, it has been shown that resveratrol suppresses IGF-1 induced cell proliferation and elevates apoptosis in human colon cancer cells, via suppression of IGF-1R/Wnt and activation of p53 signaling pathways (Vanamala et al., 2010).

Tat protein plays a pivotal role in both the human immunodeficiency virus type 1 (HIV-1) replication cycle and the pathogenesis of HIV-1 infection. A very recent study has demonstrated that resveratrol, a SIRT1 activator, attenuates the transactive effects of Tat in HeLA-CD4-long terminal repeat-β-gal cells (MAGI) via NAD(+)-dependent SIRT1 activity suggesting that this antioxidant, through the regulation of different pathways such as SIRT1 activation, could be a novel therapeutic approach in anti-HIV-1 therapy (Zhang et al., 2009).

In addition, resveratrol also induces the activation of genes that encode for proteins involved in oxidative phosphorylation and mitochondrial biogenesis processes (reviewed by Szkudelska & Szkudelski, 2010). In this context, it has been shown that resveratrol improves the functioning of mitochondria in cells. In fact, the capacity of this antioxidant to reduce mitochondrial ROS levels and to induce the biosynthesis of antioxidant molecules, like MnSOD, along with its ability to increase the activity of these antioxidant defences, has been previously demonstrated (Valdecantos et al. 2010a). These actions could also explain the protective role of this antioxidant against situations with an imbalance in the oxidative status such as steatosis, obesity etc.

2.2.3 Vitamins with antioxidant properties: Vitamin E and Vitamin C

Vitamin E is the nature´s most effective lipid-soluble antioxidant, with an important role protecting unsaturated fatty acids residues in cells membranes, which are important for membrane function and structure (Van Gossum et al., 1988). Vitamin E is only produced by photosynthetic organisms. It refers to a group of eight naturally occurring compounds α-, β-, γ-, δ- tocopherols and tocotrienols. α-tocopherol, especially the naturally occurring D-α-tocopherol, is the one with the highest biological activity (Brigelius-Flohe & Traber, 1999). This variant of vitamin E can be found most abundantly in vegetable oils such as wheat germ oil, sunflower, and safflower oils (Reboul et al., 2006). Vitamin E is also found in many foods, mainly of plant origin, especially in leafy green (broccoli, spinach), seeds, including soybeans, wheat germ, some breakfast cereals and yeast beer. It can also be found in animal foods such as egg yolk.

The role of the vitamin E has emerged as a possible therapy for decreasing ROS production or increasing the endogenous levels of antioxidants and for protecting cell membranes at an early stage of free radical attack (Horwitt, 1986). Thus, vitamin E down-regulates NADPH oxidase (Calvisi et al., 2004), which is the major source of ROS in the vascular wall and it also up-regulates eNOS activity which leads to an increase in NO production (Ulker et al., 2003). As vitamin E is a potent antioxidant with anti-inflammatory properties, several lines

of evidence suggest that α-tocopherol has also potential beneficial effects with regard to cardiovascular disease (Singh et al., 2005; Rodrigo et al., 2008). A recent study has also demonstrated that natural vitamin E analog alpha-tocopheryl phosphate (alphaTP) modulates atherosclerotic and inflammatory events through the regulation of certain genes (Zingg et al., 2010). However, it is also important to point out that the non-antioxidant activities of tocopherols may also represent the main biological reason for the selective retention of alpha-tocopherol in the body, or vice versa, for the metabolic conversion and consequent elimination of the other tocopherols (Zingg et al., 2004).

Several studies have demonstrated the beneficial effects of vitamin E on obesity and its related disorders such as diabetes. In fact, plasma vitamin E reflects the amount of α-tocopherol in the body. It is interesting to note that lower plasma vitamin E levels have been observed in type 2 diabetic patients (Skrha et al., 1999). In addition, the study from Botella-Carretero et al., (2010) demonstrated that alpha-tocopherol concentrations are inversely associated with body mass index in morbid obesity. Other study has demonstrated that vitamin E intervention increased the plasma activity of several antioxidant enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GPx) and T-AOC (total anti-oxidative capacity) whereas it is able to decrease the levels of Isoprostane 8-epi PGF2alpha, which is a product of oxidative stress that causes potent smooth muscle contraction. The same study demonstrated that vitamin E intervention also decreased plasma glucose, insulin and triglycerides level in obese rats. Therefore, this study demonstrated that vitamin E has positive effects for improvement of oxidative stress status and glucose metabolism in an animal model of diet-induced obesity (Shen et al., 2009). In this context, Manning et al., (2004) showed that vitamin E supplementation decreased plasma peroxide concentration in obese individuals. Other study showed that antioxidant supplementation with vitamin E, C and β-carotene reduced exercise-induced lipid hidroperoxide (ΔPEROX) in overweight young adults. Possible collective mechanisms to explain this finding include a shift in the cytokine profile from a pro-inflammatory to a less inflammatory profile (lowered IL-6, increased adiponectin), an attenuation of cholesterol and triglyceride levels during exercise and a small increase in total antioxidant status (Vincent et al., 2006). On the other hand, vitamin E supplementation decreased concentrations of both 8-isoprostane and lipid peroxides in overweight subjects, indicating a decrease in systemic oxidative stress (Sutherland et al., 2007). Vitamin E supplementation in patients with diabetes decreased the levels of proinflammatory adipokines, such as IL-1, TNF-α, IL-6, and reactive C protein in serum and stimulated monocytes (Devaraj & Jialal, 2000; Upritchard et al., 2000). A recent study demonstrated that supplementing alpha-tocopherol (vitamin E) and vitamin D3 in high fat diet decreases IL-6 production in murine epididymal adipose tissue and 3T3-L1 adipocytes following LPS stimulation (Lira et al., 2011). Thus, this study suggested that vitamin E and D3 supplementation can be used as an adjunctive therapy to reduce the proinflammatory cytokines present in obese patients. A significant role played by oxidative stress and lipid peroxidation in the cascade of events involved in hepatic necroinflammatory damage is supported by an experimental study, which also showed that antioxidant vitamin E reduces fatty liver in obese Zucker rats (Soltys et al., 2001). In this context, the study from Vajro et al., (2004) strengthens the view that antioxidants, and especially vitamin E, may represent a relevant therapeutic tool for the treatment of children with obesity-related dysfunction who are unable to adhere to low-calorie diets (Vajro et al., 2004).

Finally, a very recent study concludes that MitoVES, a mitochondrially targeted analog of α-tocopheryl succinate, is an efficient anti-angiogenic agent of potential clinical relevance, exerting considerably higher activity than its untargeted counterpart. MitoVES may be helpful against cancer but may compromise wound healing (Neuzil et al., 2011). However, it is important to state that there are several controversial effects of vitamin E on cancer and diabetes that will be discuss later.

Vitamin C (Vit C) or ascorbic acid is one of the non-enzymatic antioxidants that can eliminate ROS, thus preventing tissue damage (Fetoui et al., 2008). Moreover, Vitamin C is the most abundant water-soluble antioxidant in the body and acts primarily in cellular fluid having the potential to protect both cytosolic and membrane components of cells from oxidant damage (Talaulikar & Manyonda, 2011). Vit C exerts its antioxidant effects in both direct and indirect ways. In the direct way, Vit C scavenges free radicals formed (Dawson et al., 1990) or interacts with reduced glutathione (Dudek et al., 2005). As an indirect way, it helps recycling vitamin E, thus, supplying active vitamin E (Netke et al., 1997).

Vit C is present in several fruits and vegetables such as citrus fruits, tomato, strawberry, pepper, cabbage, and leafy greens. Vit C can not be stored in the body, and excess Vit C is excreted in urine (Alpsoy & Yalvac, 2011).

Over the years, it has been suggested the usage of Vit C as a remedy against many diseases ranging from common colds to several types of cancers. Moreover, it is known that there is a close relationship between Vit C supply and immune cell activity, especially phagocytosis activity and T-cell function (Strohle et al., 2011) It also contributes to the formation and health of blood vessels, tendons, ligaments, bones, teeth and gums, it helps the body to absorb iron and to recover from wounds and burns, and serious deficiency of this vitamin can lead to scurvy, which is now a rare condition in the Western world (Garriguet, 2010; Strohle et al., 2011).

It has been described that obese patients have lower mean serum concentration of Vit C being even in an inadequate Vit C status, which leads to lower serum antioxidant capacity and greater inflammatory responses (Mah et al., 2011; Aasheim et al., 2008). Thus and regarding its effects on obesity, several studies demonstrated that Vit C dietary supplementation reduced body weight in a cafeteria diet-induced obese rat model, without affecting food intake (Campion et al., 2008; Boque et al., 2009). Moreover, it has been described that Vit C increases lipolysis and decreases triglicerides accumulation by decreasing the activity of glycerophosphate dehydrogenase, a marker of adipose conversion (Hasegawa et al., 2002; Senen et al., 2002). It also has been observed that Vit C supplementation is negatively associated with the occurrence of obesity suggesting that higher waist-to-hip ratios were associated with lower plasma ascorbic acid concentrations and that Vit C depleted individuals may be more resistant to fat mass loss.

Interestingly, these beneficial effects of Vit C seem to be due to a decrease observed in uric acid levels. In fact, it is known that hominoids during the Miocene could not biosynthesize Vit C, as a key gene involved in Vit C production: L-gulono-lactone oxidase had mutated. Hence, this mutation has been proposed to increase uric acid as an antioxidant that could replace the decrease in Vit C availability that may have occurred during this period (Johnson et al., 2009). Moreover, uric acid helps to raise blood pressure, stimulate salt-sensitivity, and induce insulin resistance and mild obesity, and thereby it helps to promote

survival during a period of famine or stress which also leads to de development of obesity and its related comorbidities nowadays. Uric acid has been shown to be involved in metabolic pathways that lead to oxidative stress, endothelial dysfunction, and to a vascular and systemic inflammatory response. Moreover, the elevation in uric acid levels observed after fructose ingestion, with a consequent reduction in nitric oxide may lead to a reduced glucose uptake in the skeletal muscle, hyperinsulinemia, and insulin resistance. Thus, several clinical studies showed the beneficial effects of lowering uric acid therapies on several markers of cardiovascular and renal disease (Stellato et al. 2011). In this context and supporting this idea, Hunter et al., (2011) concluded that dietary supplementation with Vit C may confer health benefits because of increased antioxidant potential or through mechanisms resulting from increased endogenous Vit C generation or decreased serum uric acid concentrations.

In summary, Vit C is a potent antioxidant that might prevent and improve obesity and several comorbidities by different mechanisms. Besides its antioxidant power, Vit C can also exert its beneficial effects by regenerating other antioxidants such as reduced glutation or vitamin E as well as by lowering uric acid levels.

2.2.4 Selenium

Selenium (Se) is an essential trace element consumed in submilligram amounts. It is primarily found in organically bound forms in the diet. Selenium is naturally found in plants, seafood, meat and meat products. The amount of selenium that is needed to ingest to maximize plasma glutathione peroxidase (GSHPX) activity is established between 55-75 µg/d in the EU (Rayman, 2005). The element exists in both organic form of selenium, as part of selenoproteins (selenomethionine and methylated selenocompounds) as well as in inorganic forms such as selenites and selenates (Gromadzinska et al., 2008).

Selenium is required for the function of a number of key selenium-dependent enzymes (selenoproteins). Many of the known selenoproteins, in which selenium is the active site, are necessary for a wide range of metabolic processes, including thyroid hormone regulation, immune function and reproduction and they catalyze redox reactions (Kryukov et al., 2003). Because of the potential of selenoproteins to protect against oxidative stress, selenium functions as a dietary antioxidant and because of that it has been studied for its potential role in chronic diseases such as hypertension, cardiovascular disease, cancer and diabetes mellitus, as well as aging and mortality (Boosalis, 2008). In this context, experimental studies have shown that selenium has carcinostatic effects when added in high levels to the diet of animals treated with carcinogenic chemicals (Gromadzinska et al., 2008). In this context, evaluation of health claims by the FDA in the U.S. concerning the purportedly positive effects of selenium provided certain evidence for permitting a qualified health claim (Trumbo, 2005). Recent results of the SUVIMAX study showed that supplementation with vitamin C, vitamin E, β-carotene, selenium and zinc is able to reduce the rate of prostate cancer in men having normal levels of prostate-specific antigen in their plasma (Meyer et al., 2005).

Observational and interventional studies in humans have demonstrated the beneficial effect of selenium dietary intake. Thus, antioxidant supplementation contained selenium (100 mg) combined with vitamin C (500 mg), vitamin E (200 IU) and co-enzyme Q10 (60 mg) significantly alleviated the atherosclerotic damage caused by excessive production of ROS in

patients with multiple cardiovascular risk factors. This beneficial vascular effect was associated with an improvement in glucose and lipid metabolism as well as with a decrease in blood pressure (Shargorodsky et al. 2010). It has also been demonstrated that the selenium supplementation is able to decrease lipid hydroperoxides (LH) post-exercise in overweight subjects, providing preliminary evidence for a potential role of selenium as an effective antioxidant therapy to reduce oxidant stress at rest and following high-intensity exercise in high-risk population groups (Savory et al. 2011).

The mechanisms responsible for the link between selenium and prevention of diseases associated or induced by an excessive production of reactive oxygen species are currently under-known. However, there are experimental evidence of selenium compounds affecting cell growth, cell cycle, DNA repair, gene expression, signal transduction and regulation of the redox status (Gromadzinska et al., 2008). On the other hand and as mentioned before, selenium functions as part of the selenoproteins which are involved in a wide range of metabolic processes. The cellular form of glutathione peroxidase (GPx 1) was the first selenoprotein identified. Several other GPxs containing the amino acid selenocysteine (Sec; analogous to cysteine in which sulfur is replaced by selenium) have been found since then. The glutathione (GSH)-Px system is found in almost all tissues and is believed to play a part in the body's antioxidant defence protecting polyunsaturated fatty acids and proteins from the damaging effects of peroxides and lipid hydroperoxide (LH) (Halliwell B, 2007). The other two major groups of known selenoprotein enzymes are the iodothyronine deiodinases that regulate operation of thyroid hormones, and the thioredoxin reductases (TrxR), involved in catalyzing the reduction of oxidized thioredoxin and other substrates. Additional selenoprotein is the selenoprotein P, the major form of selenium in the plasma and it also acts as an antioxidant in the extracellular space by reducing peroxynitrite and phospolipid hydroperoxides and forming complexes with mercury and cadmium (Gromadzinska et al., 2008).

Therefore and to sum up, there is strong evidence that selenium and the selenoproteins play a regulatory role in the following processes, which underlines its positive effects on health (Gromadzinska et al., 2008):

- ROS-activation of protein kinases in the cytoplasm and nucleus;
- ROS-activated modification of the thiol and hydroxyl groups in the Cys and Tyr;
- Controlling changes in the cell redox potential through inducing activation of the transcriptional factors and initiating *de novo* gene expression;
- Regulating the expression of membrane and nuclear receptors responsible for cell maintenance, intercellular communication, and changes in cell growth;
- Affecting apoptosis, necrosis and cell survival processes.

2.2.5 Green tea

Green tea, a product made from the leaves and buds of the plant *Camellia sinensis*, is, after water, the second most popular beverage worldwide, and a mayor source of dietary polyphenols that are known to render a myriad of health benefits (Rietveld & Wiseman, 2003). Green tea polyphenols are generally known as catechins. These group of compounds includes epicatechin, epigallocatechin, epicatechin gallate and epigallocatechin-3-gallate (EGCG) which is the most active of the major polyphenols and primarily responsible for the effects of green tea (Stewart et al., 2005).

EGCG has a four ring structure with eight hydroxyl groups being, therefore, highly hydrophilic, exhibiting good solubility in aqueous media (Zhong & Shahidi, 2011). EGCG is also a powerful antioxidant, possessing the highest antioxidant potency among all tea catechins, and it plays a protective role against oxidative stress in biological environments. For example, EGCG induced enzymes that play important roles as cellular antioxidant defenses such as SOD and catalase. It also lowers Malonil dialdehide (a product of lipid peroxidation and, therefore, a marker of oxidative stress) and it has also the ability of interacting with singlet molecular-oxygen, superoxide, peroxyl radicals, hydroxyl radicals, and peroxynitrite (Wei & Meng, 2010). Thus, green tea consumption may also show potential preventive effects against several oxidative stress-related disorders such as cardiovascular diseases (Rickman et al., 2010; Plutner et al., 1990; Nantz et al., 2009) and several types of cancer such as breast, prostate, lung, skin, gastric and colon cancer. It also shows neuroprotective effects in Parkinson and Alzeimer's disease (Zhao, 2009), ameliorates several autoimmune diseases such as autoimmune arthritis (Kim, H. R. et al., 2008), and immune-mediated liver injury (Wang et al., 2006) or even it seems to prevent skin cell damage (Jorge et al. 2011). Furthermore, green tea (or its active biomolecule EGCG) could be one potential anti-obesogenic agent (Stefanovic et al., 2008) and might be used in the prevention and treatment of this disease. Moreover, several "*in vivo*" studies demonstrated that green tea extracts or EGCG dietary supplementation decreased both body and adipose tissue weights (Park et al., 2011; Choo, 2003; Hasegawa et al., 2003), improved insulin sensitivity and glucose tolerance (Cao et al., 2007; Serisier et al., 2008) and had beneficial effects on prevention of hypertension (Ihm et al., 2009) and modulation of plasma cholesterol (Bursill et al., 2007), conditions linked to metabolic syndrome. In addition, it lowers the incidence of streptozotocin-induced diabetes (Song et al., 2003) and reduces body weight, body fat, and blood levels of glucose and lipid in leptin receptor-defective obese rats (Kao et al., 2000).

Several mechanisms have been proposed to explain the beneficial effects of EGCG in obesity and diabetes. Thus, EGCG protects pancreatic cells (Song et al., 2003), enhances insulin activity (Dhawan et al., 2002), represses hepatic glucose production (Waltner-Law et al., 2002), reduces food uptake and absorption (Kao et al., 2000), stimulates thermogenesis by increasing the uncoupling protein 2 (UCP2) and lipid excretion (Dulloo et al., 1999; Liao, 2001), and modulates insulin-leptin endocrine systems (Kao et al., 2000). Moreover, EGCG inhibits the sodium-dependent glucose transporter (Kobayashi et al., 2000) and represses various enzymes related to lipid metabolism, such as acetyl-CoA carboxylase, fatty acid synthase, pancreatic lipase, gastric lipase, and lipooxygenase (Liao, 2001; Wang & Tian, 2001) as well as lipolytic genes such as hormone sensitive lipase (HSL) and adipose triglyceride lipase (ATGL) in adipose tissue (Lee et al., 2009). It also reduces serum- or insulin-induced increases in the cell number and the triacylglycerol content of 3T3-L1 adipocytes during a 9-day period of differentiation (Sakurai et al., 2009) and also reviewed by Liu et al. (2006). It also inhibits adipocyte proliferation (Hung et al., 2005). Moreover, EGCG suppressed the differentiation of adipocytes through the inactivation of the forkhead transcription factor class O1 (FoxO1) and sterol regulatory element-binding protein-1 (SREBP1c) which are involved in adipocyte differentiation and lipid synthesis respectively in 3T3-L1 adipocytes (Freise et al. 2010). Regarding adipocytes hyperplasia it has been described that green tea EGCG may act at different concentrations in regulating mitogenesis and apoptosis of 3T3-L1 preadipocytes by inducing a decrease in the phosphorylated

ERK1/2, which are signal elements found to modulate the mitogenic and adipogenic signaling in 3T3-L1 (Wu et al., 2005), as well as decreasing ciclin dependent kinase 2 (Cdk2) activity and protein levels. Moreover, it has also been described that EGCG inhibited the mitogenic effect of insulin on preadipocytes in a dose and time-dependent manner, and that this inhibition might be due to its suppressive effects on the activities of the insulin receptor (Ku et al., 2009). Thus, the traditional knowledge about the anti-obesity effects of green tea can be confirmed and validated by scientific evidence.

It is important to point out that the beneficial effects of EGCG in cancer, but also in obesity and related disorders, are not always due to its antioxidant nature. In fact, it has been demonstrated that EGCG contribute to the beneficial effects of green tea on diabetes, obesity, and cancer by modulating gene expression. In fact, one of the possible mechanisms by which EGCG can inhibit cancer progression is through the modulation of angiogenesis signaling cascade as EGCG treatment leads to the downregulation of genes involved in the stimulation of proliferation, adhesion and motility as well as invasion processes, but also to the upregulation of several genes known to have antagonist effects (Tudoran et al., 2011). Very recent studies have also suggested the ability of EGCG to prevent several types of cancer through epigenetic mechanisms (Berner et al., 2010; Li Y et al., 2010; Nandakumar et al., 2011).

Concerning its effects on obesity, it has been reported that EGCG reduced them RNA levels of several gluconeogenic enzymes, glucose-6-phosphatase (G6Pase) and phosphoenolpyruvate carboxykinase (PEPCK) in the normal mouse liver as well as in the intestine (Yasui et al., 2011a, b). EGCG also improves cholesterol metabolism through the up-regulation of LDL receptor and also reduces extracellular apoB levels (Goto et al., 2011). Finally, it appears that EGCG modulates body weight gain in high fat-fed mice both by increasing the expression of genes related to fat oxidation in skeletal muscle and by modulating fat absorption from the diet (Sae-Tan et al., 2011).

3. However, not everything is positive: Side effects of antioxidants

Despite the initial positive and beneficial effects observed in many studies (some of them mentioned in the first part of this chapter), not all that glitters is gold. Thus, other clinical studies investigating antioxidant effects have been often disappointing given the consistent and promising findings from experimental investigations, clinical observations and epidemiological data. In this context, there are some controversial results, especially in the field of antioxidant supplementation, cancer and cardiovascular events (and mortality associated with these events) as well as when assessing the direct effects of antioxidants on mitochondria which are the main sources of reactive species in the organism apart from NADPH oxidase in the vascular walls. In this context, clinical trials of antioxidant therapeutics in human volunteers have produced negative or inconclusive results or have shown very little benefit. The inability of clinical trials to prove the usefulness of antioxidant therapies shows the failure in translating our knowledge of molecular and cellular mechanisms into efficient clinical remedies (Firuzi et al., 2011). The reason of clinical failure of many antioxidants despite the existence of overwhelming evidence on the involvement of oxidative damage in various pathologies still remains elusive although it is interesting to note that most of these studies generally agree on the notion that antioxidants are much

more effective in prevention of disease rather than in the treatment of an already established active pathology (reviewed by Firuzi et al., 2011). In this context, we will review in the following part of the chapter some of these studies where no positive effects where found with the aforementioned antioxidants (lipoic acid, resveratrol, vitamins etc) and we will summarize some potential explanations for these controversial data.

3.1 Neutral or even deleterious effects of antioxidants

3.1.1 Lipoic acid

Some studies concerning the prooxidant potential of LA and DHLA have been performed in recent years. In fact, DHLA exerts prooxidant actions by accelerated iron-dependent hydroxyl radical generation and lipid peroxidation in liposomes, probably by reducing Fe^{3+} to Fe^{2+} (Scott et al., 1994). A study also concluded that LA and DHLA have prooxidant properties on markers of protein oxidation such as protein thiol and carbonyl in heart muscle of aging rat (Cakatay et al., 2005). In addition, DHLA stimulates MPT (mitochondrial permeability transition) by increasing production of ROS in isolated rat liver mitochondria and bovine heart submitochondrial particles (Morkunaite-Haimi et al., 2003). In this sense, Valdecantos et al. (2010a) also found that LA inhibited glutathione peroxidase activity and induced the uncoupling of the electron transport chain suggesting prooxidant actions of this antioxidant under the experimental conditions established in this study (Valdecantos et al., 2010a).

It is also very interesting to know that the beneficial role of LA supplementation in Type 2 diabetes is controversial. In one way, it has been postulated that the beneficial effects could be manifested by a mild prooxidant activity of the compound, leading to cellular adaptation against oxidative stress in addition to the attenuation of reductive stress in diabetes (Roy et al., 1997). In fact, the results derived from the study of Moini et al. (2002) pointed to the fact that the oxidized form of LA activates the insulin signal transduction pathway by acting as a prooxidant (Moini et al., 2002). Lipoic Acid increased tyrosine phosphorylation of immunoprecipitated insulin receptors, presumably by oxidation of critical thiol groups present in the insulin receptor β-subunit. Furthermore, it has been demonstrated that short-term incubation of LA in 3T3-L1 adipocytes induced glucose uptake by facilitating oxidative stress (Krieger-Brauer et al., 2000). However, long-term incubation of 3T3-L1 adipocytes with LA increased intracellular glutathione levels and inhibited the rate of glucose uptake (Mottley & Mason, 2001; Moini et al., 2002), which suggests that the duration of LA treatment is a critical step when analyzing the effects of LA on glucose uptake and insulin sensitivity. In addition, the effects of LA on adiponectin, a key adipokine involved in insulin sensitivity are also controversial, which does not help to postulate if LA beneficial actions on insulin sensitivity are mediated through this adipokine. Thus, Cummings et al. (2010) did not observe any significant change in fasting plasma adiponectin levels in fructose-fed University of California, Davis-Type 2 diabetes mellitus (UCD-T2DM) rats after dietary LA supplementation (Cummings et al., 2010). But not only the effects of LA on adiponectin are controversial, but also its actions on diabetes and obesity are questionable since several studies have not found any positive effects of this antioxidant on these disorders. Thus, supplementation with LA did not exhibit any effect on the lipid profile or insulin sensitivity of patients with diabetes type 2, with no changes in the concentrations of total cholesterol, cholesterol fractions, TG, and HOMA index (de Oliveira et al., 2011). Furthermore, LA

administered orally at this dose for 2 weeks did not protect against lipid-induced insulin resistance in overweight and obese humans (Xiao et al., 2011). In a pilot study with adolescents with type 1 diabetes mellitus LA was not an effective treatment for decreasing oxidative damage, total antioxidant status HbA1c or microalbuminuria in type 1 diabetes mellitus (Huang & Gitelman, 2008). In addition, other studies did not even observe the ability of LA to induce weight loss in obese subjects (Koh et al., 2011).

The experiment design is also another point to take into account when describing the actions of LA, as it can influence the sense of the data obtained. Thus, Volchegorskii et al. (2011) studied the correlation between the effect of α-lipoic acid, emoxipin, reamberin, and mexidol on LPO *in vitro* and the action of these drugs on insulin sensitivity and tolerance to glucose load *in vivo*. They found that the preparations producing prooxidant effect *in vitro* (α-lipoic acid and reamberin) are characterized by pronounced insulin-potentiating activity, but only slightly increase (α-lipoic acid) or even decrease (reamberin) tolerance to glucose load suggesting controversial effects depending on experimental procedure: *in vitro vs. in vivo* (Volchegorskii et al., 2011). In this sense, we have also found that LA exerted direct effects on mitochondria oxidative status in a prooxidant manner (Valdecantos et al., 2010a) whereas we also observed that LA increases hepatic mitochondrial defenses through Foxo3a in a diet-induced obesity rat model (Valdecantos et al., 2011a) corroborating the controversial actions found for this fatty acid depending on the experimental procedures.

Finally, it is important to state that the ability of LA and/or DHLA to function as either anti- or prooxidants, at least in part, is also determined by the type of oxidant stress and the physiological circumstances. These prooxidant actions suggest that LA and DHLA act by multiple mechanisms, many of which are only now being explored and it is interesting to declare that prooxidant actions does not necessary mean deleterious effects as previously described for this antioxidant. In fact, α-Lipoic acid was shown to stimulate glucose uptake into 3T3-L1 adipocytes by increasing intracellular oxidant levels and/or facilitating insulin receptor autophosphorylation presumably by oxidation of critical thiol groups present in the insulin receptor β-subunit. Thus, the real meaning of the antioxidant or prooxidant effects of LA as well as the compounds described in this chapter warrants further investigation.

Lipoic Acid has been reported to have a number of potentially beneficial effects in both prevention and treatment of oxygen- related diseases. Selection of appropriate pharmacological doses of LA for use in oxygen-related diseases is also critical apart from experimental design and duration of treatment as previously described. Thus, in further studies, careful evaluation will be necessary for the decision in the biological system whether LA administration is beneficial or harmful (Cakatay, 2006).

3.1.2 Resveratrol

As mentioned before, many beneficial effects on health have been ascribed to this molecule. However, it should be emphasised that a great deal of work has been developed in isolated cells thus limiting the extrapolation of the results to the *in vivo* situation. In this context, Pérez-Jiménez and Saura-Calixto (2008) have reviewed the *in vivo* trials published during the last 13 years (seventy five trials) were the effects of different grape products on different CVD risk factors have been evaluated (Perez-Jimenez & Saura-Calixto, 2008). Most published studies have dealt with some specific aspects of mechanisms of grape flavonoid

action or have focused only on one product, such as wine. Thus, it is important to point out that not only resveratrol actions have been evaluated in these trials but also polyphenols, alcohol and dietary fibre have been tested. In animal and human studies, grape products have been shown to produce hypotensive, hypolipidaemic and anti-atherosclerotic effects, and also to improve antioxidant status as measured in terms of plasma antioxidant capacity, oxidation biomarkers, antioxidant compounds or antioxidant enzymes. However, there are several studies where neutral and even negative effects were found regarding its effects on lipid profile and markers of oxidative stress (reviewed by Pérez-Jiménez & Saura-Calixto, 2008). It is important to underline that differences in the design of the studies and in the composition of the tested products (not always provided) could explain the different results observed and therefore these results can not been strictly extrapolated to resveratrol actions.

Despite its potential as an anti-obesity compound, data regarding the effects of resveratrol on adipokines are still insufficient to be conclusive. Adipokines are bioactive peptides produced by adipose tissue and involved in the physiological regulation of fat storage, energy metabolism, food intake, insulin sensitivity, and immune function among others. Several trials have observed that oxidative stress caused dysregulated production of adipokines (Soares et al., 2005; Kamigaki et al., 2006), therefore, it could be very important in the future to analyze the effects of resveratrol on these adipokines in an attempt to restore the optimal concentrations of those which, in turn, could lead to an improvement in obesity and related disorders.

Finally and although long-term effects of using resveratrol are still unknown, it is fair to state that this antioxidant shows a very good profile and could be a potential therapy against a wide range of diseases related to oxidative stress and aging (through SIRT1 actions), although more studies are needed in this field.

3.1.3 Vitamins E and C

Vitamins were selected for antioxidant therapy in several studies in the past decades because they were cheap and available, but they are not the best antioxidant molecules in terms of efficacy. In fact, many studies agree on the lack of evidence on the beneficial effects of antioxidant vitamins and in some cases even point to harmful effects. Thus, observational studies have reported an inverse association between vitamin E and cardiometabolic risk, but also, results from trials studying supplementation with this antioxidant failed to confirm any protective effect of them on cardiovascular disease (Devaraj et al., 2007; Wu et al., 2007).

In the review of Bjelakovic et al. (2007), 68 randomized trials conducted on 232,606 adults who were randomized to receive commonly used antioxidants including β-carotene, selenium, vitamins A, C and E were analyzed for the effect of antioxidant on all cause mortality (Bjelakovic et al., 2007). This review followed the Cochrane Collaboration method and included primary (healthy subjects) and secondary (diseased individuals) prevention studies. When all trials were considered, antioxidants did not seem to significantly affect mortality. However, when 47 "low-bias" trials were separately analyzed, β-carotene, vitamin A and vitamin E administered alone or in combination, significantly enhanced all-cause mortality whereas Vitamin C and selenium did not have any significant effect on mortality. Another meta-analysis performed on 7 large trials of vitamin E involving 81,788 individuals showed that there was no significant difference in cardiovascular mortality

when individuals receiving vitamin E were compared to control (Vivekananthan et al., 2003). In another large meta-analysis including 19 trials and 135,967subjects, it was shown that high dose intake of vitamin E (>400IU/day) may increase all-cause mortality (Miller et al., 2005). However, other authors have claimed that the increase in mortality caused by vitamin E is questionable. Large secondary prevention trials of vitamin E including Secondary Prevention with Antioxidants of Cardiovascular Disease in Endstage Renal Disease (SPACE), the Cambridge Heart AntioxidantStudy (CHAOS), the Heart Outcomes Prevention Evaluation (HOPE), Gruppo Italiano per lo Studio de lla Sopravvianzan ell'Infarto Miocardico (GISSI) have evaluated the effects of vitamin E on mortality rates. In a meta-analysis of these trials and other primary and secondary prevention trials, it was concluded that vitamin E supplementation did not significantly affect mortality or risk of cardiovascular diseases (reviewed by Firuzi et al., 2011).

Numerous assays demonstrated that vitamin E decreased atherosclerotic formation (Fruebis et al., 1995; Parker et al., 1995), however, other studies showed no effects on plasma lipids (Nagyova et al., 2002; Cyrus et al., 2003; Hasty et al., 2007) or even an increase in plasma lipids after vitamin E treatment was also observed (Crawford et al., 1998). Mechanistic studies demonstrated that the role of α-tocopherol during the early stages of lipoprotein lipid peroxidation is complex and that the vitamin does not act as a chain-breaking antioxidant (Stocker & Keaney, 2005). It is tempting to suggest that the positive or deleterious effects of vitamin E supplementation or treatment on lipid profile also depend on the population chosen, the study design, types and dosages of antioxidant, and their duration of use. All these factors make the comparison and interpretation of the studies difficult. In addition, in a very recent study, it was demonstrated that vitamin E did not perform any positive effect on heat stress in Japanese quails (Halici et al., 2011). Moreover, there are conflicting results regarding the effects of this vitamin on blood pressure (Plantinga et al., 2007; Ward et al., 2007; Rodrigo et al., 2008).

Apart from the ambiguous effects observed after vitamin E treatment on cardiovascular events and mortality, its effects on cancer are not very clear either. Thus, the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study (ATBC) and the β-Caroteneand Retinol Efficacy Trial, especially on lung cancers did not observe reduction in the incidence of lung cancer among male smokers after five to eight years of dietary supplementation with alpha-tocopherol or β-carotene. In fact, these trials raise the possibility that these supplements may actually have harmful as well as beneficial effects.

Finally, the evidence also suggests no beneficial effect of vitamin E supplementation in improving glycaemic control in unselected patients with type 2 diabetes whereas haemoglobin $A(_1c)$ ($HbA(_1c)$) (deeply involved in microvascular complications of diabetes and possibly macrovascular disease) may decrease with vitamin E supplementation in patients with inadequate glycaemic control or low serum levels of vitamin E. This shows the importance of targeting therapy. Due to the limitations of the available evidence, further studies are warranted in the field of vitamin E actions on diabetes and obesity (Suksomboon et al. 2011). On the other way and despite the beneficial effects previously described for vitamin E in obesity, there are also different studies where no significant effects of vitamin E on obesity have been found. Thus, body mass index remained unchanged in patients after 3 months of vitamin E treatment (Skrha et al., 1999; Nagyova et al., 2002; Vincent et al., 2007). Different research groups have examined de effect of vitamin E on F_2-isoprostanes (markers

of oxidative stress which are increased in obesity), and whereas some of these research groups found statistically significant reductions in F_2-isoprostanes (Kaikkonen et al., 2001; Block et al., 2008), other studies did not find any effect (Meagher & Rader, 2001; Weinberg et al., 2001). Factors that could influence these conflicting results could be the sample size, the degree of obesity and/or presence of elevated F_2-isoprostanes at baseline.

Concerning vitamin C, several studies have also showed controversial results. Thus, the National Health and Nutrition Examination Surveys (NEHENES) reported that low serum levels of Vit C were marginally associated with an increased risk of fatal cardiovascular disease and significantly associated with risk of fatal cardiovascular disease (Schleicher et al., 2009). In contrast, several studies did not find evidence for a protective effect of vitamin C against cardiovascular disease. Thus, Ramos and Martinez-Castelao., (2008) (Ramos & Martinez-Castelao, 2008) failed to demonstrate significant differences on lipoprotein oxidation between vitamin C-treated and not treated patients under haemodialysis. Moreover, other studies found that Vit C further than having benefitial effects it also could have negative effects. Thus, The Physician Health Study (Gaziano et al., 2009) illustrated that vitamin C showed neither health benefits nor safety issues, and Moyad et al., (2008) reported that increased vitamin C intake had adverse effects, such as kidney stones and iron-related disorders. Other reports suggest that it may accelerate atherosclerosis in some people with diabetes, and fail to confer benefit in patients with advanced cancer (Talaulikar & Manyonda, 2011). In fact, vitamin C also seems to have a controversial role in cancer. Thus, many papers have described that millimolar concentrations of ascorbate have a deep inhibitory effect on the growth of several cancer cell lines in vitro. Actually, it seems that such cytotoxic activity of vitamin C relies on its ability to generate reactive oxygen species rather than its popular antioxidant action. This is paradoxical but, the fact is that ascorbic acid may have also prooxidant and even mutagenic effects in the presence of transition metals (reviewed by Verrax & Calderon, 2008). In this sense, Podmore et al., (1998) discovered an increase in a potentially mutagenic lesion, following a typical Vit C supplementation suggesting that prooxidant effects might occur at doses up to 500 mg per day, although at lower doses the antioxidant effect may predominate. In this sense, it is important to mention that the type, dosage and matrix of exogenous antioxidants seem to be determinant in the balance between beneficial or deleterious effects of vit. C. Briefly, the antioxidants in fruit and vegetables may be tightly bound within the tough fibrous material of these foodstuffs and may exert their antioxidant activity not in the blood or tissues but in the gastrointestinal tract where free radicals are constantly generated from food (Kelly et al., 2008) and on the contrary, vitamins ingested as food supplements are probably digested too quickly to replicate these effects. Moreover, in many cases, the equivalent serum levels of vitamin C cannot be achieved if the supplement is given orally since there is an upper limit for absorption of vitamin C of about 500 mg, which is why this is normally the highest dose given (Monsen, 2000). No acute toxic dose has been established but chronic toxicity can occur in those with hereditary glucose-6-phosphate dehydrogenase deficiency given doses of 2 g/day of this vitamin and some of the problems that can occur include kidney stones, diarrhoea, nausea, and red blood hemolysis. There is also the possibility of dental decalcification and rebound scurvy in infants born to women consuming large concentrations of vitamin C and estrogens changes in women (Soni et al., 2010).

Table 2 (modified from Firuzi et al., 2011) shows large meta analysis of randomized controlled clinical trials exploring the efficancy of vitamins E and C in prevention of various diseases (Alkhenizan & Hafez, 2007; Polyzos et al., 2007; Bardia et al., 2008; Evans, 2008; Arain & Qadeer, 2010; Myung et al., 2010). It is important to highlight that only large studies that included at least 4000 subjects were included in this table. Based on the studies summarized in this table and putting all the former findings together, we can led to the conclusion that vitamins cannot be used as effective antioxidant therapeutics for human diseases unless more definitive and comparative studies will be carried out.

Publication	Antioxidants studied	Number of randomized participants	Illness	Results	Conclusions
Arain et al., 2010	Vitamin E	94,069	Prevention of colorectal cancer	No significant effect on prevention of cancer.	No conclusive evidence on the benefit of treatment
Myung et al., 2010	Vitamin E, vitamin C, vitamin A, β-carotene, selenium (alone and in combination)	161,045	Prevention of cancer	No significant effect on prevention of cancer. No significant effect according to the type of antioxidant or type of cancer. Significant increase in the risk of bladder cancer in a subgroup meta-analysis of 4 trials.	No conclusive evidence on the benefit of treatment
Evans et al., 2008	B-carotene and α-tocopherol	23,099	Prevention of age related macular Degeneration (AMD)	No significant effect on prevention or delaying the onset of AMD (all trialsincluded). No significant effect when the analyses were restricted to either β-carotene or α-tocopherol.	No conclusive evidence on the benefit of treatment
Bardia et al., 2008	β-carotene, vitamin E, selenium	104,196	Prevention of cancer and mortality	Significant increase in cancer incidence and cancer mortality among smokers by β-carotene.	Selenium may be beneficial

Publication	Antioxidants studied	Number of randomized participants	Illness	Results	Conclusions
				Vitamin E supplementation had no effect. Selenium supplementation might have anticarcinogenic effects in men and thus requires further research.	
Alkhenizan et al., 2007	Vitamin E	167,025	Prevention of cancer	No significant difference in all-cause mortality, cancer incidence and cancer mortality. Significant reduction in the incidence of prostate cancer.	Beneficial for prostate cancer prevention. Not beneficial for other causes
Polyzos et al., 2007	Combination of vitamin C and vitamin E	4,680	Prevention of preeclampsia	No significant effect on the risk of preeclampsia, fetal or neonatal loss, or small for gestational age infant.	No conclusive evidence on the benefit of treatment

Table 2. Large meta analysis of randomized controlled clinical trials exploring the efficacy of vitamins E and C in prevention of various diseases.

3.1.4 Selenium

Despite the beneficial effects previously mentioned regarding this antioxidant, it is important to note that only selenium-deficient individuals may benefit from selenium supplementation, because such supplementation in selenium-replete individuals may even cause higher risk of diseases such as cancer (Brozmanova et al., 2010). Selenium has a narrow therapeutic window and there is considerable inter-individual variability in terms of metabolic sensitivity and optimal selenium intake. In fact, optimal intake for any individual is likely to depend on polymorphisms in selenoprotein genes that may also affect the risk of disease. Moreover, the baseline levels of each subject could determine the beneficial effect of the selenium intake (Stranges et al., 2010). For instance, no additional benefit of supplementation (even up to 300 μg/d) was found in an elderly population with mild hypothyroidism where selenium status was adequate prior to the start of supplementation (Rayman et al., 2008). High–selenium diets may stimulate the release of glucagon, promoting hyperglycaemia, or may induce over-expression of GPx-1 and other antioxidant selenoproteins resulting in insulin resistance and obesity (Stranges et al., 2010). Moreover,

the increase in developing diabetes or adverse lipid profile among the participants in the NHANES 2003-2004 study could be associated to their high plasmatic selenium levels (137 mg/L) (Laclaustra et al., 2009).

Although the underlying mechanisms that could explain the detrimental effects of high selenium are not fully understood yet, they could involve DNA damage and oxidative stress induction resulting in apoptosis (Brozmanova et al., 2010). Therefore, due to a broad interest to exploit the positive effects of selenium on human health, studies investigating the negative effects such as toxicity and DNA damage induction resulting from high selenium intake are also highly required (Brozmanova et al., 2010). Moreover, urgent need for personalized risk prediction with regard to cancer and other diseases prevention and treatment activities of selenium supplementation is highly suggested (Platz & Lippman, 2009).

3.1.5 Green tea

EGCG is regarded as the most active catechin in green tea, but, in spite of its reported favorable effects, conflicting results have been reported from epidemiological studies (Boehm et al., 2009) and EGCG appears to act both as an anti-oxidant as well as a prooxidant agent as previously described for lipoic acid.

In this context, Elbling et al., (2005) concluded that excessive EGCG concentrations induced toxic levels of ROS *in vivo*, and moreover, they found *in vitro* DNA-damaging effects at pharmacological concentrations. Thus, hepatic and intestinal toxicities associated with the consumption of high doses of green tea preparations were reported in animal studies. Furthermore, EGCG mediated mitochondrial toxicity and ROS formation was implicated as the possible mechanism for the cytotoxicity to isolated rat hepatocytes and hepatotoxicity in mice (Galati et al., 2006). Another study found that higher intake of green tea might cause oxidative DNA damage of hamster pancreas and liver and also found that the major cytotoxic mechanism found with hepatocytes was mitochondrial membrane potential collapse and ROS formation (Takabayashi et al., 2004). Moreover, Yun et al. (2006) clarified that EGCG acts as a prooxidant, rather than an antioxidant, in pancreatic β cells *in vivo,* suggesting that consumption of green tea and green tea extracts should be monitored in certain patients. Thus, it should be considered that the effects of green tea and its constituents may be beneficial up to a certain dose, and higher doses may cause some unknown adverse effects similarly as what has been observed with selenium.

The harmful effects of tea overconsumption are due to three main factors: its caffeine content, the presence of aluminum, and the effects of tea polyphenols on iron bioavailability. Caffeine is the world's most popular drug and can be found in many beverages including tea. One reason for the popularity of caffeine-containing beverages is the stimulation of the central nervous system that they provide (MacKenzie et al., 2007). However, caffeine may have other effects, including metabolic and hormonal ones. With short-term dosing, caffeine has been shown to impair glucose metabolism in nondiabetic persons (Greer et al., 2001; Johnston et al., 2003) and in persons with type 2 diabetes mellitus (Lane et al., 2004; Robinson et al., 2004). The effects on other hormonal systems have not been as well investigated. However, cortisol levels may increase after short-term administration of caffeine in healthy subjects or in those with elevated blood pressure (Lovallo et al., 1996). Regarding green tea aluminium content, several studies described that the negative effect of

green tea decoction, arises from the high absorption of aluminium released in the decoction. Some analogies in the competition mechanism between aluminium and iron will be obtained in human nutritional conditions; the regular green tea decoction consumption could constitute an important additional source of dietary aluminium. Then, it could have, in a long term, a negative consequence on iron status and erythropoiesis toxicity, particularly in patients with high iron requirements or with chronic renal failure like hemodialysis (Marouani et al., 2007). It is also interesting to mention that an iron–catechin complex formation can cause a significant decrease of the iron bioavailability from the diet (Hamdaoui et al., 2003). Moreover, it has been shown that bioactive dietary polyphenols inhibit heme and non-heme iron absorption in human intestinal cells mainly by reducing basolateral release of iron (Kim, E. Y. et al., 2008).

3.2 Why many antioxidants have failed to show efficacy in interventional human studies? Some explanations

The most simple explanation for the controversial studies found is that not all antioxidants behave in the same way or with the same intensity, at least when their direct actions on mitochondria are analyzed as demonstrated in the study from Valdecantos et al. (2010a). Thus, the outcomes found with different antioxidants should be carefully examined since the physical properties of the assayed molecules are different and could affect their ability to enter the mitochondria and, therefore, to affect their functionality, although other mechanisms different from pure physical characteristics of the compounds can not be rule out.

Some of the antioxidants are ineffective and nonspecific and dosage regimen or duration of therapy was inefficient. Thus, several points should be taken into account before making general conclusions. Thus, the fact that the antioxidant molecule could have low bioavailability should also be considered when planning a trial. In this context, some polyphenolics, especially green tea catechins, may have very low bioavailability (Williamson &; Manach, 2005). Thus, optimization of these molecules has been suggested to improve this outcome, but, it is still under investigation. Other point that should also be taken into account is that the antioxidant could have poor target specificity, that the reaction products of the antioxidant could be toxic, that a single antioxidant is not enough to overcome oxidative stress and therefore a combination of several antioxidant compounds is needed or the fact that certain antioxidants are not effective in well-nourished populations (deeply reviewed by Firuzi et al., 2011).

Other possible reasons relate to patient cohort included in trials, that patients do not equally benefit from antioxidant therapy, the trial design itself and the usage of inappropriate or insensitive methodologies to evaluate oxidative state which underlines the urgent need for the development of sensitive and specific biomarkers to correctly assess the oxidant status of patients. Furthermore, oxidative stress is not always the primary cause of the disease and, therefore, it is not the only cause of the disease (reviewed by Firuzi et al., 2011).

4. Conclusion

There has been much enthusiasm in the field of oxidative-stress related disorders and nutritional approaches to improve health. Antioxidants have been advocated for therapy of a vast range of serious diseases in the 1980s and 1990s. Furthermore, the tendency to add

bioactive compounds such as antioxidant molecules in foods to improve consumer health, which has been very strong during the past decade, will increase significantly in the future, in parallel with a growing awareness of the impact of food components on human health. However, in the light of recent negative findings, many doubts have now been raised about the usefulness of administration of single antioxidants. What seems to be clear is that although there are many dietary antioxidants and all of them can act as "antioxidant" molecules, not all behave in the same way. Thus and as described in this chapter, some of them seem to have potential as therapy against several diseases (resveratrol) whereas there are other molecules whose results are not very promising (vitamins C and/or E). Thus, once we apply our experience to select the right disease and the right population, design optimized and highly bioavailable antioxidants directed at specific and appropriate targets and choose optimal treatment times, duration and doses, useful therapeutics could emerge for various diseases. On the other hand, as possible negative interactions with antioxidants may rely on the dose consumed by each person, natural antioxidants from natural foods in a balanced diet such as the Mediterranean diet arise as the best way to implement these substances in regular nutrition instead of consuming them as supplements.

Since there are not yet adequately validated markers of the onset, progression and/or regression of any oxidative stress associated chronic diseases there is the urgent need in sorting out which markers or combinations of markers are predictive of human diseases. Ideally one would wish to demonstrate that modulation of a biomarker by a specific antioxidant intervention is predictive of modulation of incidence of some major chronic disease endpoint in humans. To accomplish this, further investigation is also needed.

Furthermore, inhibition of ROS production through the development of inhibitors against the main sources of ROS generation offers an alternative approach to conventional antioxidant therapies due to their controversial results. Thus, NADPH oxidase, as the main source of ROS production in endothelial cells and directly involved in hypertension and cardiovascular disease, has been suggested as a potential target for decreasing ROS generation. A number of clinically important drugs used for the treatment of hypertension, hypercholesterolaemia and coronary artery disease such as the statins, AT1 (angiotensin II receptor type 1) antagonists and ACE inhibitors have been shown to decrease NADPH oxidase-derived superoxide and ROS production. In this context, one area of investigation that has been the focus of much recent interest in the past years is to address mitochondria, and more specifically, to analyze the potential beneficial effects of modulating mitochondrial ROS generation in order to treat or prevent the development of several oxidative-stress associated disorders (reviewed by Pérez-Matute et al., 2009). Again, more studies are needed in this regard.

Finally, and as described in the review from Prieto-Hontoria et al. (2010), the mechanisms by which antioxidant components modulate obesity, cancer and other oxidative stress related disorders are not fully understood, partly because of the lack of appropriate research tools to identify the complex mechanisms involve. With the emergence of Nutrigenomics, it is now possible to exploit genome-wide changes in gene expression profiles related to molecular nutrition. Evolution of `omics´ such as epigenomics, transcriptomics, proteomics and metabolomics will allow a better understanding of how dietary antioxidants may affect both energy metabolism, carcinogenesis etc leading to healthier foods and, in turn, healthier people and lifestyles.

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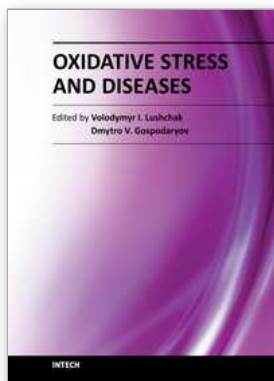
Oxidative Stress and Diseases

Edited by Dr. Volodymyr Lushchak

The development of hypothesis of oxidative stress in the 1980s stimulated the interest of biological and biomedical sciences that extends to this day. The contributions in this book provide the reader with the knowledge accumulated to date on the involvement of reactive oxygen species in different pathologies in humans and animals. The chapters are organized into sections based on specific groups of pathologies such as cardiovascular diseases, diabetes, cancer, neuronal, hormonal, and systemic ones. A special section highlights potential of antioxidants to protect organisms against deleterious effects of reactive species. This book should appeal to many researchers, who should find its information useful for advancing their fields.

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