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Effect of Fruit and Vegetable Intake on Oxidative Stress and Dyslipidemia Markers in Human and Animal Models

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1. Introduction

In the last 40 or 50 years mankind, particularly in the western world, has modified its diet to include a reduced amount of fruits and vegetables, while increasing its intake of processed foods with a high content in fats and simple carbohydrates. This change has brought on consequences such as the development of a vast array of conditions like the metabolic syndrome (also known as syndrome X or insulin resistance syndrome), which is known to include dyslipidemia and oxidative stress among other physiologic disturbances, and be itself a risk factor for the development of diabetes and cardiovascular disease (CVD). On the other hand, studies suggest that a diet rich in fruits and vegetables can have a positive impact on dyslipidemia and oxidative stress markers, as well as other components of the metabolic syndrome. These positive effects are mediated mainly by the antioxidant vitamins (A, C and E), carotenoids, polyphenols and other important phytochemicals.

2. Diet, the metabolic syndrome, dyslipidemia and oxidative stress

In 2007, the World Health Organization (WHO) estimated that about 1.7 billion people worldwide were overweight (including at least 155 million children) (Hossain et al., 2007), these numbers have transformed obesity and its related maladies into a worldwide epidemic. Even though obesity is almost always assumed to be a necessary condition for the development of dyslipidemia, metabolic syndrome, diabetes and CVD, and these terms are sometimes used as if they all occur alongside each other, this may not always be true, since overweight people may in fact present normal lipid and glucose concentrations, as well as normal blood pressure, normal insulin metabolism and low inflammatory markers (Barter et al., 2007) (the term marker in this chapter is to be understood as measurable markers such as cholesterol concentration and not genetic markers). Therefore it is the clustering of factors

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defined as metabolic syndrome that confers the highest risk for CVD mortality, although many of the isolated conditions are also risk factors for CVD (Isomaa et al., 2001).

Since diet is a major contributor to metabolic syndrome, some authors have noted the particular relationship between the two. Fructose has been consumed mainly from fruits and honey at about 16-20 g/day since early times, while having a recent and significant increase to 85-100 g/day with the addition of high-fructose corn syrup (HFCS) as a sweetener in products such as soft drinks, fruit juices and many other items commonly included in western diets; this rise in consumption has important metabolic consequences for the individual (Basciano et al., 2005). When adequate amounts of fructose are ingested it can have a positive effect on glucose metabolism, like the reduction in glycemic response and a better tolerance to glucose, however, when fructose is ingested in greater quantities it directs the liver (the main organ responsible for metabolizing it) to increase *de novo* lipogenesis, in other words, it deviates the metabolism in favor of storing energy in the form of triacylglycerols while increasing their plasma levels, which in turn translates into obesity and insulin resistance, all of which part of the metabolic syndrome (Basciano et al., 2005).

A high fat diet can also have important effects on the individual, including induction of oxidative stress. A study compared the effects of the consumption of a high fat breakfast (fast food style) in patients with metabolic syndrome, to a meal recommended by the American Heart Association (control). An increase in triacylglycerols, with a concomitant decrease in HDL, was found in the fast food breakfast group; at the same time, biomarkers of oxidative stress rose significantly in this group compared to the control (Devaraj et al., 2008). These effects have also been noted on animal models, for example, when New Zealand White rabbits were subjected to a diet rich in cholesterol for six months their lipid profiles changed; their triacylglycerols, total and LDL cholesterol rose while HDL cholesterol was reduced; oxidative stress markers were also elevated when cholesterol was administered in the diet, these effects were not apparent when coconut or sunflower oil were administered instead of cholesterol (Sabitha et al., 2010). The aforementioned experiments show how dyslipidemia and oxidative stress can occur simultaneously as consequences of a high fat diet; however this apparently simple relationship can become more intertwined thereafter, since the products of oxidative stress can oxidize lipid-containing molecules such as LDL to form oxLDL (which can be considered a marker of oxidative stress), and in turn, generate an inflammatory response. The organism cannot cope with these extenuating circumstances for an extended period of time and cardiovascular disease takes place (Rizzo et al., 2009). It is therefore possible to argue that initially both conditions take place side by side, and after a while the two become part of the same cumulative disorder, in which oxidative stress can synergize with altered lipid levels and aid in the development of cardiovascular disease. Sachidanandam in 2009 (Sachidanandam et al., 2009) shows that in rats fed a high fat diet, the collagen patterns were altered favoring matrix accumulation, as well as increased constriction and impaired relaxation of the vascular tissue (Sachidanandam et al., 2009). Similar results were obtained in mice by Poirier in 2005, who reported that a high fat diet can lead to the development of obesity, insulin resistance and other symptoms similar to metabolic syndrome in humans (Poirier et al., 2005). This evidence shows that the dyslipidemia and oxidative stress (initially brought on by diet) can lead to the development of CVD by impacting specific tissues like the arteries.

Dyslipidemia is so called because it involves a high serum triacylglycerol concentration (≥ 200 mg/dL), low high-density lipoprotein cholesterol (HDL) concentration (< 35 mg/dL), small dense low-density lipoproteins (sdLDL) and an increased concentration of inflammatory markers (Adiels et al., 2008; Barter et al., 2007; Bestehorn et al., 2010; Rader, 2007). The first three biomarkers have even been referred to as the "lipid triad", and because they have been found in patients with CVD, it is also called the "atherogenic lipoprotein phenotype" (Bestehorn et al., 2010; Grundy, 1998; Rizzo & Berneis, 2005).

Oxidative stress can be described as an imbalance in the REDOX homeostasis of the cell, although it lacks a precise definition. Under normal circumstances the cell produces an assortment of oxidant molecules that can become extremely detrimental if their concentrations are not kept under strict regulation and whose elimination takes place via enzymatic and non-enzymatic systems. The synthesis of these oxidant molecules, usually known as reactive oxygen species (ROS) is an unfortunate byproduct of having an aerobic metabolism and underlies the so called oxygen toxicity (Auten & Davis, 2009). Nevertheless, the cell has an impressive array of defense mechanisms that, in healthy individuals and under an optimal diet, can be quite effective in maintaining ROS under adequate concentrations. This balance of oxidation and reduction can be a fragile one, and when it is broken cells and tissues are led to oxidative stress. This can occur by an acute or chronic overproduction of ROS brought on by trauma, toxicity (by the consumption of ethanol, cigarette smoke, xenobiotics and others), genetic factors, stress, poor or unhealthy eating habits (something already acknowledged) and many other factors (Augustyniak & Skrzydlewska, 2009; Studzinski et al., 2009; Talukder et al., 2011). It can also be caused by a deficient antioxidant defense system even if the oxidative molecules are present in normal quantities. In any case, this brittle balance is overwhelmed to the side of the oxidative molecules, and it is at this point where the negative effects can become apparent in the progression of CVD as well as other conditions like different types of cancers, diabetes and the progression of aging (Agalliu et al., 2010; Gupta et al., 2010; Kenyon, 2010). Another interesting point is that oxidative stress is a condition that cannot be completely neutralized, since there is constant damage being inflicted on the cell from its own metabolism as well as environmental sources (Costantini & Verhulst, 2009).

Oxidative stress is a complex condition, and it can affect the organisms in many different ways, there are various ways that it can be measured; these can be grouped into four general categories: free radical production, antioxidant mechanisms, oxidative damage and repair mechanisms (Monaghan et al., 2009).

Thiobarbituric acid reacting substances (TBARS) is one of the most popular techniques used to evaluate oxidative stress in living organisms (Alturfan et al., 2009). It is also used to evaluate oxidation of food systems. TBARS are used to determine malondialdehyde (MDA) and other molecules that are generated as byproducts of lipid oxidation, (it is therefore a measure of oxidative damage) although it can be somewhat unspecific since other compounds also react with thiobarbituric acid (Caprioli et al., 2011).

Antioxidant capacity of plasma can also be used as a marker of oxidative stress or REDOX status of live systems. A number of methods are used to measure plasma antioxidant capacity, some of the most popular are ferric reducing ability of plasma (FRAP), oxygen radical scavenging capacity (ORAC), total radical-trapping antioxidant parameter (TRAP) and trolox equivalent antioxidant capacity (TEAC) among others (Grigelmo-Miguel et al., 2009).

Other indicators of oxidative stress or REDOX status include activity and expression of antioxidant enzymes and concentration of non-enzymatic antioxidants in plasma and tissues (Beltowski et al., 2008).

2.1 Oxidative stress and antioxidants

The main molecules implicated in the occurrence of oxidative stress are free radicals and ROS. Free radicals are defined as species having one or more unpaired electrons which make them unstable and highly reactive. Among the most common oxygen free radicals are the superoxide anion ($O_2^{\cdot -}$), the hydroxyl radical ($^{\cdot}OH$) and peroxyl radicals ($ROO^{\cdot}$). Other kinds of ROS are not free radicals, the most important one being hydrogen peroxide (H_2O_2). The sources of the $O_2^{\cdot -}$ are dioxygen-reducing enzymes such as NADPH oxidases, xanthine oxidase, monoamine oxidase, prostaglandin synthases (Peyrot & Ducrocq, 2008) and cytochrome P450-dependant oxygenases, some of which are located in the cell membrane of polymorphonuclear cells, macrophages and endothelial cells (Turrens, 2003). The mammalian mitochondria complexes I and III have been shown to produce $O_2^{\cdot -}$, however, these are not the only sites inside the mitochondria that produce it, the others are mainly enzymes that interact with the matrix NADH pool and/or the CoQ pool (Murphy, 2009). Non-enzymatic sources of the anion have also been reported, mainly by the action of coenzymes (flavins), prosthetic groups (iron-sulfur clusters) or enzyme-reduced xenobiotics (adriamycin) (Turrens, 2003).

Some of the negative effects that ROS can exert is DNA and RNA damage which can lead to an increased number of mutations, membrane lipid peroxidation, and protein tyrosine nitration (this last one being a marker for so called nitrosative stress), and after the cell sustains too many of these insults, it may become mutated or direct itself to apoptosis, giving way to the development of the previously mentioned oxidative stress-related diseases, like CVD, cancer diabetes and aging (Corpas et al., 2008). Some ROS molecules are, under certain conditions, non-toxic, but can react with other free radicals such as $NO^{\cdot}$, to form the peroxynitrate ion (Corpas et al., 2008; Peyrot & Ducrocq, 2008; Valko et al., 2007):

$$NO^{\cdot} + O_2^{\cdot -} \rightarrow ONOO^- \quad (1)$$

This reaction has been known to take place in situations such as hyperglycemia, atherosclerosis, inflammation and others, while at the same time modulating important signaling pathways such as the one mediated by the serine/threonine protein kinase Akt, which is involved in cell growth, glycogen synthesis, cell proliferation and apoptosis (Song et al., 2007). Since the production of ROS is largely inevitable, the cell has evolved mechanisms to cope with them and maintain an acceptable REDOX state, they can be divided into two broad groups; enzymatic and non-enzymatic.

The enzymatic antioxidant mechanisms are sensitive to the REDOX state of the cell, and are thus activated when an overproduction of free radicals starts to become a threat to the wellbeing of the cell. Their function is to neutralize a free radical or potentially toxic molecule by either converting it to an innocuous compound, or to another one that is less reactive and/or less toxic. Among them are superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPX), glutathione reductase (GR) and glutathione-S-transferase (GST). These enzymes work in synergy with non-enzymatic compounds, such as phytochemicals, obviously ingested in the diet.

SOD (E.C. 1.15.1.1) is an enzyme whose function is to catalyze the dismutation of the $O_2 \cdot -$ into H_2O_2. This important reaction has been known to take place on both the cell's interior and exterior, mediated however by different isoenzymes. SOD1 is present in the cytosol, nucleus and intermembrane space in the mitochondria; it is also called the Cu/Zn SOD because it requires these two metals in order to be catalytically active. SOD2 is dependent not on Cu/Zn but on Mn, and it is found on the mitochondrial matrix. SOD3 contains Cu and it is found on the extracellular matrix of tissues, being therefore called EC-SOD (Gao et al., 2008; Juarez et al., 2008; Wilcox et al., 2009). These enzymes play an important role in maintaining the $O_2 \cdot -$ concentration in a range of about 10^{-10} M, nevertheless they do it by transforming it into H_2O_2 that is still toxic; it is at this point that CAT and GPX becomes active. Catalase (E.C. 1.11.1.6) is a heme-containing enzyme that is almost ubiquitously expressed in aerobic organisms. It is an oxidoreductase that is capable of converting the toxic H_2O_2 into water and molecular oxygen without the parallel synthesis of free radicals, a critical feature since H_2O_2 itself may have been formed from the $O_2 \cdot -$; a free radical. It is also known for having one of the fastest catalytic rates (~ 10^7 M/s) (Goyal & Basak, 2010; Odajima et al., 2010; Prakash et al., 2009). GPX (E.C. 1.11.1.9 and 1.11.1.12) is another enzyme that also performs a similar function as CAT, while at the same time having broader substrate range, therefore being able to remove other organic peroxides and converting them into water and the corresponding alcohols while utilizing glutathione as an electron donor. GPX is a family of enzymes that may be Se-dependent (in the form of a selenocysteine); and in mammals there are four isoenzymes. GPX1 is found in all tissues, and is abundant in erythrocytes, liver, lungs and kidneys; GPX2 or gastrointestinal GPX is found in the gastrointestinal tract, GPX3 is present in plasma, and GPX4, or phospholipid GPX is ubiquitous, as GPX1, but is selective towards lipid hydroperoxides (Arsova-Sarafinovska et al., 2009; Margis et al., 2008). When the toxic hydroperoxides have been neutralized by GPX, glutathione is oxidized in the process and in order to return it to its reduced state, GR (E.C. 1.8.1.7) must participate at this time. GR is a flavoprotein capable of reducing glutathione by oxidizing NADPH, therefore contributing to maintaining a pool of reduced glutathione and helping to preserve the REDOX state of the cell (Marty et al., 2009; Meister, 1988). Finally, GST (E.C. 2.5.1.18) is a family (containing at least the α, μ, ω, π, θ, and ζ isoforms) pertaining to the Phase II detoxification enzymes. They are responsible for transferring glutathione to electrophilic molecules of diverse nature, such as xenobiotics, environmental toxins, a number of drugs and of course products of oxidative stress; thereby making them less reactive and easier to excrete (Burmeister et al., 2008; Carlsten et al., 2008; D. M. Townsend & Tew, 2003; Danyelle M. Townsend et al., 2009). All of these enzymes work in unison to maintain the ROS and free radicals under tolerable concentrations; a simplified scheme of how they do so is exemplified in Fig. 1

Although the enzymes are quite efficient in maintaining the cell's REDOX state they must be aided by non-enzymatic molecules. These can be of endogenous (glutathione) and of exogenous origin (ascorbate, tocopherols, carotenes, retinols and polyphenols among others) and their functions are to neutralize free radicals by either acting on their own or in conjunction with the enzymatic systems. Glutathione is a tripeptide (γ-glutamyl-cysteinylglycine) synthesized in the cell by a two-step process involving γ-glutamyl cysteine synthetase and glutathione synthetase, both of which are ATP-dependent. This molecule is found in the millimolar concentration range in the cytoplasm and within many organelles. Since it has a thiol functional group, it can become oxidized and reduced and thus function

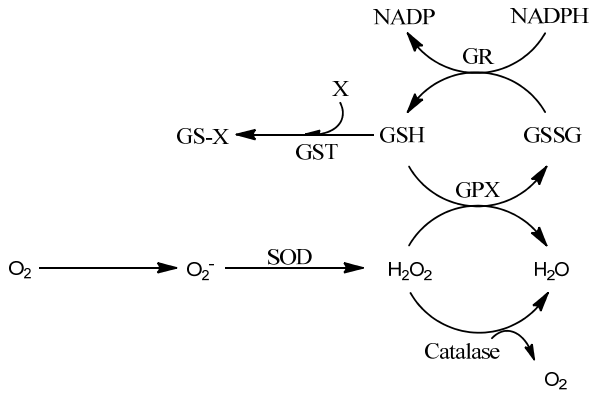

Fig. 1. The relationships between the different enzymatic antioxidant mechanisms. GR: glutathione reductase; GSH: reduced glutathione; GSSG: oxidized glutathione; GPX: glutathione peroxidase; SOD: superoxide dismutase; X: xenobiotic; GS-X : glutathione-conjugated xenobiotic. Equations are not balanced.

as an antioxidant, donating an electron and sacrificing itself to neutralize ROS in addition to many other molecules of diverse natures. The neutralization of oxidative molecules can take place without an enzymatic component by a direct interaction of the oxidant and the antioxidant, but when other molecules such as hydroperoxides are involved, an enzymatic system such as GPX is crucial to the process. Since reduced glutathione is oxidized during the course of these reactions, the enzyme GR is in charge of maintaining the pool of reduced glutathione consuming NADPH (from the pentose phosphate shunt) in the process. There are plasma membrane transporters that can also modulate the cell's REDOX state by importing and exporting reduced glutathione, oxidized glutathione and many conjugates of glutathione. The depletion of glutathione can be an important indicator of oxidative stress via the ratio of reduced to oxidized glutathione (Ballatori et al., 2009; Diaz Vivancos et al., 2010; Foyer & Noctor, 2011; Martin & Teismann, 2009).

Ascorbate, also known as vitamin C, is one of the exogenous molecules obtained through the diet. It is present in a diverse variety of vegetable foodstuffs such as apples, papaya, mango, guava oranges and others (Oliveira et al., 2010; Suárez-Jacobo et al., 2011). It is known as a free radical scavenger that does not act as a pro-oxidant under normal conditions, and it has been mentioned to function in parallel with glutathione (Cuddihy et al., 2008; Foyer & Noctor, 2011; Frei & Lawson, 2008; Valero et al., 2009). Because of its ability to neutralize free radicals it has been mentioned as having a possible therapeutic use in disorders such as ischemic stroke, Alzheimer's, Parkinson's and Huntington's diseases (Harrison & May, 2009), and it is sometimes consumed by athletes to neutralize the ROS produced during exercise (Gomez-Cabrera et al., 2008), it can neutralize protein radicals (Domazou et al., 2009) and its role in the improvement of endothelial function (a precursor of atherogenesis) has also been noted (Frikke-Schmidt & Lykkesfeldt, 2010; May & Qu, 2011; Sabharwal & May, 2008).

Vitamin E is the collective term for at least eight structurally related molecules: four tocopherols and four tocotrienols, of which α-tocopherol is the most studied (Ravaglia et al.,

2008). Since tocopherols are of non-polar nature, their main function lies in the hydrophobic environment of cell and organelle membranes, protecting these structures from free radicals and also by stabilizing them (Atkinson et al., 2008; Naumowicz et al., 2009). Tocopherols induce a protective effect against oxidative stress linked to metabolic syndrome as well as other sources (Chung et al., 2010; Devaraj et al., 2008; Grattagliano et al., 2008; Roberts & Sindhu, 2009).

Carotenoids are other important molecules with antioxidant activity. They are hydrophobic vegetal pigments derived from isoprenoid units with up to 15 conjugated double bonds (Costantini & Moller, 2008; Tanaka et al., 2008). This large family of molecules contains more than 700 different structures identified so far, and are thought to play an essential role in the life cycle of the plants that produce them (Nishino et al., 2009; Tanaka et al., 2008). Even though some animals like birds, fishes and invertebrates use them in order to generate colorations for structures such as their skin and feathers, none of them have the ability to synthesize them and must therefore obtain them from exogenous plant sources. Of the most relevant ones we find α and β carotene (the later one being the one with the most provitamin A activity, and also one of the most thoroughly studied), lutein, lycopene, zeaxanthin and β-cryptoxanthin (Britton & Khachik, 2009; Costantini & Moller, 2008). These pigments have been shown to interact with virtually all the radicals present in biological systems and are, consequently, significant antioxidants. In animals they have the potential to not only act upon free radicals, but also to modulate critical functions such as immunostimulation, and inhibition of the tumorigenesis process (Krinsky & Yeum, 2003; Nishino et al., 2009).

The last exogenous antioxidant to be mentioned is retinol (Vitamin A), a molecule that is related to the previously mentioned carotenoids. β-carotene can in fact be transformed to retinol, and this can in turn be transformed into retinal and retinoic acid, all of which have different biological functions on many tissues (Bremner & McCaffery, 2008). This compound, as well as its other metabolites, affects important processes such as immunity, reproduction, growth, development and, perhaps its best known function, it holds a vital role in the visual cycle (Pasquali et al., 2008; Redmond, 2009; Redmond et al., 2010). β-carotene has been characterized as an antioxidant, nevertheless, it can have toxic effects and has been named as a pro-oxidant when it is administered at higher doses and on certain types of cell cultures (Pasquali et al., 2008; Roehrs et al., 2009). When it functions as an antioxidant it has been positively linked to diverse ailments related to oxidative stress, such as diabetes (Ramakrishna & Jailkhani, 2008), obesity (Botella-Carretero et al., 2010), low sperm motility (Kao et al., 2008), hearing loss (Michikawa et al., 2009) and others.

Aside from the "antioxidant vitamins" the polyphenol group is another very diverse family of molecules present in fruits and vegetables. They are plant secondary metabolites that can be subdivided into many groups according to their molecular structure. Some of the representative molecules included here are quercetin, coumaric acid, proanthocyanidins resveratrol among others. Although traditionally considered antioxidants, they can also have antimicrobial, antiviral and anti-inflammatory properties (Ignat et al., 2011); they have consequently gained attention because of these *in vivo* health-promoting properties (Brisdelli et al., 2009; Chong et al., 2010; Huang et al., 2010; Massaro et al., 2010).

Since fruits and vegetables are rich in all types of exogenous antioxidant molecules, scientists have linked these bioactive molecules to the positive health effects of a fruit and

vegetable-rich diet. However, fruit and vegetable intake cannot be replaced by a single antioxidant molecule or supplement; that is, ingesting vitamins or polyphenols in a purified form is not the same as acquiring them from the diet, since other nutrients present in fruits and vegetables may synergize with each other in order to elicit an effect (Liu, 2004).

2.2 The role of vegetable foodstuffs

Up until this point we have established that diet can have a profound impact in the development of conditions like oxidative stress and dyslipidemia, which are in turn related to metabolic syndrome and CVD. We have also defined oxidative stress and the ways the cell protects itself from it, and described some of the molecules which may be found in fruits and vegetables that contribute to mitigate oxidative stress in animal cells and tissues. The discussion now turns to the *in vivo* effects of fruits and vegetables, and the scientific evidence that shows their potential role (either positive, negative or neutral) on human health as well as on animal models.

There are epidemiological studies which underlie the relationship between the consumption of vegetable foodstuffs with a number of positive health effects. One of those is a sixty year follow up study that associates the consumption of fruits during childhood with a protective effect against cancer in adulthood (Maynard et al., 2003). Other authors have noted the link between consuming plant-derived products with a reduced risk for developing CVD and other non-communicable diseases (Liu, 2004), while some have found a correlation between a diet containing fruits and vegetables with a lower LDL concentration in both men and women (Djousse et al., 2004). Although most of the evidence supporting a cardioprotective effect of fruit and vegetable consumption comes from observational epidemiological studies, many of these studies have reported either weak or non significant associations (Dauchet et al., 2009). These weak associations may indicate that, aside from consuming fruits and vegetables, other factors may contribute to their positive health effects, for example, people who regularly consume fruits and vegetables tend to smoke less, exercise more and be better educated than those who do not (Dauchet & Dallongeville, 2008). Therefore, diet would not be the only factor for the prevention of CVD; exercise, smoking and drinking habits, genetic variability and many other influences must surely impact on heart health (Dauchet et al., 2009). In addition to epidemiologic studies, many dietary interventions have been carried out focused on individual fruits, vegetables or bioactive molecules isolated from them, in order to establish a direct effect of those particular foodstuffs on specific markers of health and disease. Table 1 briefly lists some experiments which have measured the effect of fruits and vegetables on oxidative stress and dyslipidemia markers in human and animal models.

From the first two studies shown in the table, it can be assumed that strawberries have the ability to regulate both dyslipidemia and oxidative stress markers. In the study by Jenkins et al., a very high dose of fruit (1 lb. daily) was administered to patients in a cholesterol-lowering diet. Strawberries improved the oxidative stress markers but had no effect on dyslipidemia markers additional to the cholesterol-lowering diet alone. Although it can be argued that such a regimen would seldom be followed by a healthy subject with a non-restrictive diet, the authors claim that this was actually a point in their favor since the inclusion of strawberries made the cholesterol-lowering diet, which limits or prohibits the ingestion of certain items, more palatable (Jenkins et al., 2008). This diet would therefore be a viable option in patients who may complain about the dullness in flavor of their available

Fruit or Vegetable	Model	Effect on dyslipidemia markers	Effect on oxidative stress markers	Author
Strawberries	Human subjects on a cholesterol lowering diet	- TC, LDL, and TAG	↓ TBARS and LDL oxidation	(Jenkins et al., 2008)
Strawberries	Human subjects with metabolic syndrome	↓ TC, LDL and small LDL particles		(Basu et al., 2010)
Different berries	Human subjects	- TC and TAG ↑ HDL	↑ Vitamin C and polyphenols	(Erlund et al., 2008)
Blueberries	Male pigs	↓ TC, LDL and HDL. - TAG		(Kalt et al., 2008)
Mango	Normolipidemic human subjects	↓ VLDL and TAG	↑ Plasma AC	(Robles-Sánchez et al., 2011)
Crude mango pulp extract	Male albino mice		↓ ROS ↑ SOD1, CAT, GR and GST	(Prasad et al., 2008)
Mango extract	Hyper-cholesterolemic mice		↓ Mitochondrial oxidative stress	(Pardo-Andreu et al., 2008)
Grape seed oil	Rats	↓ TC, LDL and atherogenic index		(Kim et al., 2010)
Grape seed extract	Rats on a hyperlipidemia-inducing diet	↓ TC, LDL and VLDL ↑ HDL	↑ Enzymatic and non-enzymatic AOX systems	(Thiruchendura n et al., 2010)
Grape seed proantho-cyanidins	Rats on a high-fat diet	↓ TAG, LDL Modulated gene expression		(Quesada et al., 2009)
Grape seed proantho-cyanidins	Healthy human subjects		↑ Plasma AC	(Natella et al., 2002)
Banana	Healthy human subjects	↑ TAG - TC	↓ Lipid peroxides	(Yin et al., 2008)
Banana polyphenols	Rats	↓ TC, TAG, free fatty acids, ↑ HDL		(Vijayakumar et al., 2009)
Turmeric and garlic	Type 2 diabetic human subjects with dyslipidemia	↓ TC, LDL and TAG		(Sukandar et al., 2010)
Garlic and aged black garlic	C57BL/KsL mice		↓ TBARS ↑ SOD, GPX and CAT	(Lee et al., 2009)
Garlic extracts	Type 2 diabetic human subjects with dyslipidemia	↓ TC and LDL ↑ HDL - TAG		(Ashraf et al., 2005)

Fruit or Vegetable	Model	Effect on dyslipidemia markers	Effect on oxidative stress markers	Author
Tomato juice	Healthy human subjects	↓ TC	↓ TBARS	(Jacob et al., 2008)
Tomato extract	Rats		↓ TBARS ↓ Glutathione depletion and tissue damage	(Jamshidzadeh et al., 2008)
Spinach and tomato	Healthy human subjects		↑ Lymphocyte intracellular carotenoid concentrations ↑resistance to H_2O_2	(Porrini et al., 2002)
Broccoli sprouts	Healthy human subjects	↓ TC and LDL ↑ HDL (in women)	↓ Plasma phosphatidil choline hydro peroxides, urinary 8 isoprostane and 8-hydroxy deoxy guanosine	(Murashima et al., 2004)
Orange juice, apples and pears	Smokers and non-smokers	↑ TC, LDL, HDL in non-smokers. ↓ TC and LDL in smokers (higher initial values)	↑ Plasma AC in non-smokers. - Plasma AC in smokers	(Alvarez-Parrilla et al., 2010)
Potatoes	Rats	↓ TC and TAG	↑ Plasma, urine and tissue AC ↑ Vitamin E	(Robert et al., 2008)

Table 1. Different studies on fruit and vegetable consumption, and their effect upon dyslipidemia and oxidative stress markers in human and animal models. – indicates no difference, ↓ decrease, ↑ increase. TC, total cholesterol; TAG, triacylglycerols; AC, antioxidant capacity; AOX, antioxidant.

eating options. In another study done by Basu et al., they administered a more modest dose of strawberries (2-3 cups daily) to obese patients with metabolic syndrome and found that this lower dose of strawberries modulated dyslipidemia markers in a positive way by decreasing cholesterol, LDL and LDL particles (Basu et al., 2010). This second study was a randomized controlled trial, in which patients continued with their regular diet and lifestyle, strawberries were added as a drink and water was used as a control. Therefore, it can be argued that the large dose of strawberries used in the study of Jenkins showed no further improvement on the lipid markers because the dyslipidemia of those patients was already controlled. In contrast, the patients in the study of Basu did not receive any additional treatment for their dyslipidemia, making the strawberries' effects more prominent.

To further scrutinize the family of berries, Erlund et al., administered an assortment of them to human subjects and detected no effect on total cholesterol or triacylglycerols, a fact that may be put aside by an important (5 %) increase in HDL. They also determined that the concentrations of vitamin C and polyphenols in plasma were increased, and, although they did not measure plasma antioxidant capacity, it seems likely that ascorbate and polyphenols would have had a positive effect on this marker (Erlund et al., 2008). Another study with berries, specifically blueberries, was done on pigs and found a decrease in total cholesterol, LDL and HDL, while having no effect on triacylglycerols. While the cholesterol lowering effect is a positive one, a reduction in HDL is not, since the decrease in this molecule is a feature of dyslipidemia (Kalt et al., 2008). Taken together these studies suggest that berries have the ability to influence lipid metabolism in a complex manner, depending on the model of study, the type of berry and the specific lipid. Effects may be regarded generally as positive or non-existing, for example triglycerides, total and LDL cholesterol might be reduced or unaltered. Only in one study, preformed in pigs, a negative result was observed as a reduction in HDL. Berry consumption showed a consistent improvement of different oxidative stress markers, although very few studies evaluated them. The effects of strawberries (as well as other berries) may be mediated by their high content of compounds such as α-carotene, vitamin C and phenolic antioxidants (ellagic-acid, proanthocyanidins, quercetin, kampferol, anthocyanins, p-coumaric acid and others), which give them their characteristic bright color (Azzini et al., 2010; Pineli et al., 2011).

Mangoes have also been found to have an effect on both humans and animals. Robles et al., administered mangoes to healthy human subjects and found a decrease in both triacylglycerols and VLDL particles, while at the same time increasing plasma antioxidant capacity; in other words, they can have a positive effect upon dyslipidemia and oxidative stress markers (Robles-Sánchez et al., 2011). Since this effect was demonstrated in healthy adults, it can be argued that mangoes can be an important tool in preventing the onset of CVD, that is, they can be a preventive measure rather than a remedial one. Previous studies on mango consumption were done in mice, showing a positive effect on different markers of oxidative stress. Prasad et al. (2008), using an extract from the pulp of the mango in mice, suggested that the decrease in the production of ROS molecules in the prostate could be related to a protective role of this extract against prostate cancer, since its onset has been linked to oxidative damage when the REDOX balance is altered. The previously stated effects of mangoes can be attributed to the many antioxidant molecules present in the fruit, namely, antioxidants such as β-carotene, vitamins C and E and polyphenols (particularly mangiferin xanthone) (Masibo & He, 2008; Shah et al., 2010).

The antioxidant potential of mango extracts has been tested on several *in vitro* and cell-based assays. Ajila & Rao (2008) found that mangoes can protect the cell lipids and proteins from oxidative damage induced by H_2O_2 in erythrocytes; the cells morphology was also preserved, which indicates the major role of this fruit´s antioxidant activity in live cells (Ajila & Rao, 2008). Mangiferin, a polyphenolic antioxidant particularly abundant in mango, has been shown to inhibit the generation of O_2^- in polymorphonuclear cells and in hypoxanthine-xanthine oxidase cell-free system; this result may pinpoint the precise enzymatic system affected by mangoes in whole organisms (Peyrot & Ducrocq, 2008). In mice, mangiferin protected mitochondria from oxidative stress, another finding of crucial importance since these organelles are the main source of oxidant molecules as a normal consequence of aerobic metabolism.

Grapes are an important crop grown commercially for winemaking as well as to be processed into juice; after they have been manufactured the seeds may be discarded but are sometimes further treated to make grape seed oil. The effects of the oil have been studied in rats; it was established that the oil has the ability to reduce total cholesterol and LDL (Kim et al., 2010). Another study notes similar results in the same animal model using grape seed extract. They showed that the extract is capable of inducing not only a decrease in cholesterol and LDL, but also in VLDL while increasing HDL and antioxidant systems (Thiruchenduran et al., 2010). This last observation may be explained by the fact that the compounds present in the seeds, namely phenolic acids, anthocyanins and proanthocyanidins, are of antioxidant nature, however the relationship between the phenolic antioxidants and the modulation of serum lipids is still not well understood.

In order to clarify this issue, the role of grape seed proanthocyanidins has been further studied in a rat model in which the animals were fed either a standard diet or a high fat diet (that the authors dub the cafeteria diet). After 13 weeks on this diet, the animals were subdivided into two groups, one of which consumed grape seed proanthocyanidins extract. It was determined that the treatment normalized plasma triacylglycerol and LDL levels, while also decreasing fatty liver (Quesada et al., 2009). The authors also evaluated the expression of some genes related to hyperlipidemia, like the SREBP1 (sterol regulatory element binding protein 1), DGAT2 (diacylglycerol O-acyl transferase 2) and MTP (microsomal transfer protein) genes, all of which are involved in the synthesis of VLDL, free fatty acids and triacylglycerols. Those genes were found to be overexpressed by the cafeteria diet and normalized with the proanthocyanidins, which in turn contributed to the stabilization of the lipid profile. Therefore this study suggests a possible mechanism of action of these phenolic phytochemicals in modulating lipid levels. Proanthocyanidins (in the form of commercially-available capsules; Leucoselect) are also capable of reducing postprandial oxidative stress in healthy human subjects after ingesting a meal rich in oxidized and oxidizable lipids (Milanese meat). Immediately after a meal is ingested the individual's antioxidant status is expected to change, one way this can be determined is by measuring LDL's susceptibility to become oxidized; this susceptibility was lower in the antioxidant-enriched meal than the control one, albeit, not statistically significant (Natella et al., 2002). Although the results in this study were not statistically significant, other publications have determined a significant effect over LDL's susceptibility to oxidation. Chopra, et al. found that after supplementing smoker's and non-smokers diets with green (β-carotene and lutein-rich) or red (lycopene-rich) vegetables for a period of 7 days, the red vegetables significantly reduced LDL's susceptibility to oxidation (Chopra et al., 2000). Stein, et al. showed that patients with coronary artery disease (CAD) who consumed grape juice for a period of 14 days reduced their LDL's susceptibility to oxidation as well as presenting an improvement in other parameters (Stein et al., 1999). Another publication by Upritchard, et al. found similar results; they supplemented the diet of type 2 diabetic patients with tomato juice, vitamin E or vitamin C and found that after four weeks of this regimen LDL's susceptibility to oxidation was significantly decreased. The effect was more prominent with tomato juice and vitamin E; vitamin C however, showed no such effect which the authors attribute to the fact that lycopene and vitamin E are both non polar and therefore transported by LDL, while vitamin C is water soluble and does not get incorporated into LDL (Upritchard et al., 2000). Contrasting these publication with the one by Natella indicates that phytochemicals can have an effect in a short period of time,

however, not statistically significant, while other authors report a significant effect on longer timeframes (7 days, 14 days and 4 weeks); which may indicate that the phytochemicals present in the consumed foodstuffs may require subsequent doses in order for their effects to become more evident.

The effect of bananas, one commonly consumed fruit in the western world, in short term regulation of plasma lipid levels and oxidative stress has also been explored. In one study, healthy subjects drank a single banana-containing drink and after two hours their triacylglycerol levels rose, while plasma lipid peroxidation was decreased; it was also shown that LDL was more resistant to oxidation after the treatment, suggesting that bananas were capable of excreting a short-term antioxidant effect *in vivo* (Yin et al., 2008). The effect of bananas is apparently due to the flavonoids they contain; an experiment done with rats estimates the effect these phytochemicals may have on the medium or long-term lipid metabolism. The animals were fed a banana-derived polyphenol-enriched diet for a period of 45 days, after this time it was found that cholesterol, phospholipids, free fatty acids and triacylglycerols in various tissues were lowered, as well as an increase in HDL (Vijayakumar et al., 2009). Although these results suggest the flavonoids are exerting a hypolipidemic effect, it should be noted that a dose over 5 mg/100 g of body weight/day of polyphenols resulted in an increase in cholesterol, mediated (at least in part) by an increase in 3-hydroxy-3-methyl-glutaryl-CoA reductase activity (HMG CoA) in the liver, an enzyme responsible for cholesterogenesis, meaning the rate of cholesterol synthesis seemed to be amplified. Even so the overall effect of a banana-rich diet tended to a total cholesterol reduction, explained by an increase in lecithin-cholesterol acyltransferase (LCAT) activity, an enzyme that removes tissue cholesterol in order to degrade it; bile acids and neutral sterols in the feces were also increased. This experiment points to a possible role of banana flavonoids in regulating lipid metabolism in favor of a total cholesterol decrease; however, it also indicates the importance of regulating the ingested doses, due to the possibility of finding dose-dependent negative effects.

Garlic has been used in herbal medicine to treat various ailments for centuries. A study administered turmeric and garlic in combination in the form of capsules of the extracts prepared to obtain the main bioactive compounds to determine their effect on type 2 diabetes mellitus patients that also presented dyslipidemia. The patients were divided in three groups that ingested 1.2, 1.6 or 2.4 g extract/day (groups A, B and C respectively). It was found that after eight weeks of treatment, group A significantly decreased their total cholesterol concentration, while LDL also decreased, although the change was not statistically significant. After 10 and 12 weeks groups A and C respectively showed a significant increase in HDL. Two of the groups (B and C) decreased their triacylglycerol concentrations, but once again it was not statistically significant (Sukandar et al., 2010). The authors of this study suggest that the observed effects could be related to the ability of the compounds present in garlic to inhibit liver lipogenic or cholesterogenic enzymes, and also by delaying lipid absorption in the gastrointestinal tract. Turmeric on the other hand may affect cholesterol catabolism by means of an increase in the activity of cholesterol 7a-hydroxylase activity, hindering cholesterol synthesis by inhibiting HMA CoA reductase, increasing the levels of LDL receptors (which aid in its elimination from blood) and by inhibiting dietary cholesterol absorption. This study points out a fact not previously mentioned, how two (or more) foodstuffs can interact with one another in order to synergize a particular effect, that is, both turmeric and garlic may have hypolipidemic effects by

themselves but taking them together may improve this effect. Garlic and aged black garlic have also been studied in an animal model of type 2 diabetes, mice were fed diets containing 5 % of either garlic of aged black garlic for a 7 week period; it was determined that the animals' hepatic TBARS were significantly decreased with the treatments; being the aged black garlic group levels significantly lower than both the control group and the garlic group. Hepatic SOD and GPX activities were significantly increased by both treatments while CAT was significantly increased in the aged black garlic group. These results indicate garlic may also have antioxidant effects as determined by an increase in the hepatic endogenous antioxidant systems, being the aged black garlic the one with the most effect. The better *in vivo* antioxidant effect of aged black garlic may be related to its higher *in vitro* antioxidant activity (4.5 times higher TEAC value). One of the most important bioactive compounds found in garlic is γ-glutamyl cysteine, which is converted to alliin and then to allicin by alliinase upon crushing, cutting, chewing of dehydrating the bulb (Pal et al., 2006); this last compound has also been studied by other authors. In an article by Ashraf, they administered 300 mg garlic tablets (or a placebo to the control group) containing 1.3 % allicin twice daily to type 2 diabetic human subjects with newly diagnosed dyslipidemia for a 12 week period. After the treatment they found a significant reduction in total cholesterol and LDL with a simultaneous increase in HDL, triacylglycerols were not affected. They explain that the effect of the garlic extract may be due to the presence of allicin and note the importance of the delivery method used to administer this compound.

Tomatoes are grown commercially for the preparation of many different products, one of which is tomato juice. The consumption of this beverage was able to reduce total cholesterol and TBARS in healthy human subjects (Jacob, 2008) indicating a positive effect of this vegetable product in both dyslipidemia and oxidative stress. Furthermore, it was established by Jamshidzadeh that a tomato extract can have cell protecting effects against drug-induced toxicity in rats, that is, it can reduce TBARS, prevent glutathione depletion and tissue damage (Jamshidzadeh et al., 2008). These experiments seem to highlight the antioxidant-promoting ability of tomatoes, something that has been linked by some authors to lycopene, an important carotenoid molecule present in them.

The role of lycopene was established in a study where the purified compound was administered in capsules to healthy humans, they found lymphocyte DNA damage was reduced, but without significantly affecting other markers of oxidative stress or antioxidant health (Devaraj et al., 2008). The effect of lycopene and other carotenoids has also been analyzed *in vivo*. Porrini et al., found that after ingesting a tomato and spinach diet the intracellular concentrations of the three main carotenoids present in both foodstuffs (lutein, β-carotene and lycopene) were significantly increased in lymphocytes (Porrini et al., 2002). At the same time, vegetable puree consumption provided the cells with an increased resistance to oxidative damage from H_2O_2. However there was no correlation between the cell's lycopene concentration and its resistance to oxidative damage. The authors conclude that even though vegetables rich in carotenoids are considered to elicit an antioxidant effect, it is yet to be clarified if that antioxidant capacity is related to carotenoids or to other molecules; it is also possible that the relationship is not simple and cannot be described with a linear model. Another possible explanation to these results is that carotenoids do not behave like direct antioxidants, but rather act by stimulating the cell's endogenous enzymatic antioxidant mechanisms such as CAT or GPX, both of which are capable of

removing H_2O_2; in other words, these molecules may be acting on a genetic level to stimulate the cell's own defense systems.

Murashima et al., studied the effects of broccoli sprouts upon metabolism and oxidative stress markers of healthy human subjects. They found that after a week of consuming 100 g/day of fresh broccoli sprouts total and LDL cholesterol concentrations were significantly lower and HDL was increased but only in the female subjects, the triacylglycerol concentration of three subjects shifted to a normal concentration (out of six who had abnormal values). Oxidative stress markers were also affected as determined by a reduction in phosphatidylcholine hydroperoxides, 8-isoprostane (a product of non-enzymatic tissue phospholipid oxidation) and 8-hydroxydeoxyguanosine (a product of oxidative DNA damage). This study remarks how gender differences in lifestyle and dietary habits, as well as hormonal levels can influence how the individuals respond to a treatment such as this one; and highlights how heterogeneous a response may be within a population.

Similar observations were made by Alvarez-Parrilla et al., (2010) who investigated the effect of consuming orange juice, a pear and an apple in both smokers and non-smokers healthy adults. They found that in non-smokers total cholesterol, LDL and HDL were significantly increased, while in smokers initial cholesterol and LDL values were higher than those of non-smokers, but after the intervention significantly decreased to values similar to those of non-smokers; triacylglycerols were not affected in either group. Plasma antioxidant activity (measured by the ORAC and FRAP techniques) was also differently affected by the dietary intervention: in non-smokers it was either increased (ORAC) or not affected (FRAP), while in smokers it was not affected (ORAC) or decreased (FRAP) (Alvarez-Parrilla et al., 2010). This studied suggested that plasma antioxidant activity was not a sensitive marker to detect oxidative stress in smokers and that the habit of smoking can be an important variable that can alter the way the phytochemicals present in fruits and vegetables interact with the individual and affect health-related physiological responses. This can once again point to how synergy occurs not only among the items that we eat but also with other environmental stimuli.

The interaction between carbohydrates and phytochemicals, and their effect on lipid levels and antioxidant status has also been studied. A recent study determined the effect of consuming a diet containing simple carbohydrates (sucrose), one of complex carbohydrates (starch) and a third containing complex carbohydrates and antioxidant micronutrients (potatoes) in a rat model. It was found that after consuming the diets for a period of three weeks, the animals' plasma and liver cholesterol levels were significantly lower with the potato-based diet; the triacylglycerol levels in the liver were also decreased. The plasma antioxidant levels were also increased. This study suggests that simple carbohydrates initiate liver *de novo* lipogenesis which in turn increases plasma triacylglycerol levels, an effect that is avoided when carbohydrates are ingested in the form of starch from potatoes, which in addition to carbohydrates contain other important non-energetic micronutrients. Some of the reported micronutrients from potatoes are vitamins C and E, carotenoids and phenolic acids, which may account for the *in vivo* antioxidant effect of this vegetable. In addition to starch and antioxidants, potatoes contain fiber in the form of resistant starch, molecules that have the ability to induce the fecal excretion of cholesterol, bile acids and other lipids, another mechanism that may explain the observed hypolipidemic effect.

3. Conclusion

Regular consumption of a fruit and vegetable rich diet has undeniable positive effects on health, although the markers to evaluate these effects are sometimes hard to demonstrate. We analyzed the effects of fruit and vegetable consumption on dyslipidemia and oxidative stress markers, two hallmarks of metabolic syndrome and CVD risk, among other diseases. We have found mostly positive effects of certain fruit and vegetable products. Interestingly, the effects can be found after short term (hours) and midterm (several weeks) interventions; and they are, in general, more clearly related to attenuating oxidative stress than to regulating lipid levels, in fact the effects of fruit and vegetable products on lipid levels are heterogeneous, usually positive or non-existent. We may conclude that oxidative stress markers are useful tools to evaluate the effects of a fruit and vegetable rich diet, however since oxidative stress is a complex condition, several markers should be analyzed in order to provide a better understanding of it. Dyslipidemia markers are probably more valuable for assessment of risk groups that for healthy individuals. In some cases the effects of fruit and vegetable consumption can be traced to a specific molecule(s) and the mechanisms of action of these compounds seem to involve regulation of gene expression. However, since food is not made up of individual molecules but rather a vast number of them, it makes sense that the isolated compounds won't have the same effect as eating the whole fruit or vegetable, because the different bioactive molecules present in the foodstuff can interact with one another and with innumerable cell targets; therefore, altering their individual bioactive properties. It is highly difficult to describe the biochemical mechanisms of action of whole fruit or vegetable products. Moreover variation in individual responses to food-derived phytochemicals is also great in human populations due to genetic and environmental variations. Consequently, the search for these factors may help to better understand how to take advantage of the many potential benefits of a healthy diet rich in fruits and vegetables.

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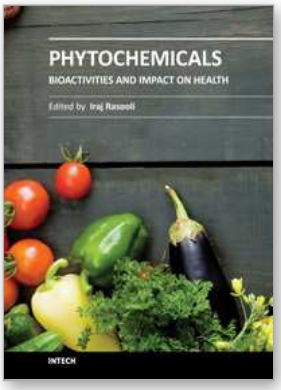

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Among the thousands of naturally occurring constituents so far identified in plants and exhibiting a long history of safe use, there are none that pose - or reasonably might be expected to pose - a significant risk to human health at current low levels of intake when used as flavoring substances. Due to their natural origin, environmental and genetic factors will influence the chemical composition of the plant essential oils. Factors such as species and subspecies, geographical location, harvest time, plant part used and method of isolation all affect chemical composition of the crude material separated from the plant. The screening of plant extracts and natural products for antioxidative and antimicrobial activity has revealed the potential of higher plants as a source of new agents, to serve the processing of natural products.

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