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Dietary Antioxidant Properties of Vegetable Oils and Nuts – The Race Against Cardiovascular Disease Progression

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1. Introduction

Cardiovascular disease (CVD) is a substantial and growing problem in most of the developing regions of the world. Evidence from experimental, clinical and epidemiological studies has unequivocally pointed to oxidative stress as the key culprit in the pathogenesis of CVD [1, 2]. CVD continues to remain a concern in developed countries and is a growing health concern worldwide. Although death rates from CVD have decreased in many countries due to advances in the field of medicine, the prevalence of CVD risk factors continues to increase. Diet is a centrally important, modifiable risk factor in the prevention of CVD [221-224].

The protection offered by foods is probably mediated through multiple beneficial nutrients contained in these foods, including mono- and polyunsaturated fatty acids, antioxidant vitamins, minerals, phytochemicals, fibre and plant protein. In dietary practice, healthy plant-based diets do not necessarily have to be low in fat. Instead, these diets may include unsaturated fats as the predominant form of dietary fat (e.g., fats from natural vegetable oils and nuts).

Consistent evidence suggests that diets rich in fruit and vegetables and other plant foods are associated with moderately lower overall mortality rates and lower death rates from chronic diseases including CVD [3- 6]. The 'antioxidant hypothesis' proposes that vitamin C, vitamin E, carotenoids and other antioxidant nutrients offer protection against CVD by decreasing oxidative damage [7-9]. As evidence began to mount from animal studies and human epide-

miological studies on the potential protective effects of antioxidants, excitement in both the lay and medical communities also began to increase.

There has been a global increase in the use of medicinal plants that contain significant amounts of antioxidant-rich oils, offering multiple health benefits with fewer side effects compared to their synthetic counterparts. The idea is that natural compounds, if taken in supplement form, may offer a broad and inexpensive means of decreasing the risk for CVD. Natural products, such as vegetable oils and nuts, may be viewed as a cocktail of active ingredients that often have a synergistic effect on health. The (n-3) PUFAs have been shown in epidemiological and clinical trials to reduce the incidence of CVD. Large-scale epidemiological studies suggest that individuals at risk of coronary heart disease (CHD) benefit from the consumption of plant and marine derived (n-3) PUFAs, although the ideal intake is presently unclear. Overall, in view of the prevalence of CHD, consumption of (n-3) PUFA oils should be considered as a useful complementary option for the amelioration of CVD. Several researchers have shown encouraging findings on the protective effects of some vegetable oils and nuts. However, more research needs to be done with regards to the nutrients in these vegetable oils and nuts to elucidate the protective effects against CVD progression. This chapter focuses on the beneficial roles of antioxidant-rich vegetable oils and nuts in the management of CVD, their mechanisms of action and future prospects.

The term "cardiovascular disease (CVD)" encompasses the major clinical end-points related to the heart and vascular system, including ischaemic myocardium (heart failure and angina), myocardial infarction (heart attack), cerebrovascular disease (stroke), high blood pressure (hypertension), peripheral arterial disease (ischaemia of the limbs), arrhythmias, congenital heart disease and rheumatic heart disease. The facts are unequivocal and disturbing; CVD is the leading cause of death worldwide [10-12].

Chronic diseases are disorders with a long duration and generally slow progression. They comprise four major non-communicable diseases (NCDs) as listed by the World Health Organization (WHO), namely CVD, cancer, chronic respiratory disease and diabetes [13], which are now reaching epidemic proportions in low- and middle-income countries (LIMIC) of the world [14-18]. NCDs constitute the major global health burden of the 21st century [19-20] without discriminating among age groups [21]. Chronic diseases are implicated in 35 million deaths annually worldwide and a large portion of these deaths occurs due to CVD in LIMIC [22].

There is a rising epidemic of NCDs in sub-Saharan Africa (SSA). However, as in other LIMICs, individuals in SSA suffer from the dual burdens of infectious disease and NCDs [22, 23]. Walker and colleagues [24] reported that SSA continues to suffer under the weight of infectious diseases such as HIV and malaria, as well as high rates of undernutrition. Facing these issues in conjunction with the chronic diseases that accompany high rates of overnutrition is a daunting task [25] for the health burden in Africa. SSA has a disproportionate burden of both infectious and chronic diseases compared with other parts of the world [26]. South Africa (SA) is a country of great diversity extending from highly industrialized cities with an urban advanced-economy lifestyle to remote rural areas with more traditional lifestyles. SA, like many SSA countries, is not immune to the NCD epidemic accompanied by the continued burden of undernutrition. In SA, approximately 28% of deaths annually are attributed to

infectious diseases, while NCDs account for 25% of the lives lost [27]. The burden of diseases related to NCDs is predicted to rise substantially in SA over the next decade if necessary measures are not in place to combat the trend [28]. WHO estimates the burden from NCDs in SA to be two to three times higher than that in developed countries [13].

Approximately 35-65% of all deaths worldwide occur due to CVDs and death rates exceed these estimated figures owing to malnutrition and infections [29, 30]. CVDs and their risk factors are increasing in SSA [17, 31] with a high prevalence of ischaemic heart disease among men in their sixties followed by women of the same age group [17]. The common potential risk factors for NCDs are tobacco use, physical inactivity and an unhealthy diet, which all lead to CVD, diabetes and cancer [32, 33]. This burgeoning epidemic of NCDs has many root causes. Additional perpetuators of these epidemics are globalization and urbanization [34-37] with abdominal obesity contributing significantly to CVD in the SSA region [38]. Compelling evidence demonstrates a rise in mortality and morbidity from the NCDs in all strata of South African society. Leeder and colleagues [39] estimated that even without changes in the risk factor profile or the mortality rates from CVD, the demographic changes will result in a doubling of the number of cardiovascular deaths in SA by 2040. Chronic diseases such as CVD, obesity and diabetes have therefore become at least as important as infectious disease.

In summary, CVD is a substantial and growing problem in most of the developing regions of the world. The burden of NCD on the African continent and in SA in particular continues to demonstrate the potential for a sustained rise. A significant investment in the health care system and in particular the primary health care system is therefore justified. Further innovative strategies and plans are needed to address the determinants of this disease burden. However, indications still point to the paucity of community-based studies aimed at investigating NCD prevalence, incidence and risk factors. Consistent evidence suggests that diets rich in fruit and vegetables and other plant foods are associated with moderately lower overall mortality rates and lower death rates from chronic diseases including CVD [3-6]. The 'antioxidant hypothesis' proposes that carotenoids, polyphenols, vitamin C, vitamin E and other antioxidant nutrients afford protection against CVD by decreasing oxidative damage [7-9]. As the evidence began to mount from animal studies and human epidemiologic studies on potential protective effects of antioxidants, excitement in both the lay and medical communities also began to increase. The idea that natural compounds, if taken in supplement form, may offer a broad and inexpensive means of decreasing the risk for CVD and other age-related diseases is a very attractive hypothesis. Enthusiasm has grown to the point where people around the globe have become aware of the need to consume a diet with a high content of fruit and vegetables.

Indeed, evidence from experimental, clinical and epidemiologic studies has unequivocally pointed to oxidative stress as the key culprit in the pathogenesis of CVD [1, 2, 40, 41]. CVD continues to remain a significant problem in developed countries and is a growing health concern worldwide. Although death rates from CVD have decreased in many countries, due to advances in the field of medicine, the prevalence of CVD risk factors continues to increase. Diet is a centrally important, modifiable risk factor in the prevention of CVD [221-224].

2. Can vegetable oils and nuts be the natural solution for CVD?

Oxidative stress is common in many clinically important cardiac disorders, including ischae-mia/reperfusion (I/R) injury, diabetes and hypertensive heart disease [42-46]. Several animal models suggest that when endogenous anti-oxidant systems are compromised, as is the case under oxidative stress conditions, exogenous antioxidant supplementation can be used for preventive and/or therapeutic intervention of CVD [42, 43, 47-49].

2.1. Composition and health benefits of vegetable oils

2.1.1. Dietary fats

Fats are the most concentrated form of energy for the body. They also aid in the absorption of fat-soluble vitamins (A, D, E and K) and other fat-soluble biologically active components [50]. Chemically, most of the fats in foods are triglycerides, made up of a unit of glycerol combined with free fatty acids, each of which may be the same or different. Other dietary fats include phospholipids, phytosterols and lipoproteins associated with cholesterol [50-52]. A balanced diet, including oils and fats that supply energy and essential fatty acids is needed for good health.

The different types of fatty acids are the most important characteristics of dietary fats. According to the degree of unsaturation (double bonds and hydrogen content), fatty acids are largely classified into three major types: saturated fatty acids, monounsaturated fatty acids (MUFA) and polyunsaturated fatty acids (PUFA). A fourth form, the trans fatty acids, are mainly produced by partial hydrogenation of polyunsaturated oils in food processing but also occur naturally in animal foods in small amounts [53].

Fatty acids consist of a hydrocarbon chain with a hydrophobic methyl group at one end and a hydrophilic carboxyl group at the other end. Greek letters (α, β, γ, ω) have been used to identify the location of the double bonds in fatty acids. The "alpha" carbon is the carbon closest to the carboxyl group. The methyl group of the molecule is also referred to as the omega end and the terminal carboxyl group is located at the delta end. Current chemical numerical terms number the carbon chain form one to "n", with n being the last carbon at the methyl end. The terms "n" and "omega" are synonymous [54].

2.1.2. Saturated fat

Saturated fatty acids contain no double bond; they are fully saturated with hydrogen. The main saturated fatty acids are lauric acid (C12:0), myristic acid (C14:0), palmitic acid (C16:0) and stearic acid (C18:0). Saturated fats are found in animal-based products, such as milk, cream, butter and cheese, meat from most land animals, palm oil and coconut oil, as well as manu-factured products made from these, such as pies, biscuits, cakes and pastries [55].

2.1.3. Monounsaturated fat (MUFA)

MUFAs are predominant in vegetable oils, such as olive oil, canola oil and peanut oil and are also found in high proportions in animal fats [56]. Much of the interest in the role of MUFA in

the prevention of coronary heart disease (CHD) stems from the observed beneficial effects of the Mediterranean diet [57], which includes high consumption of olive oil. MUFAs are less susceptible to oxidation when compared to PUFAs. This in turn leads to increased availability of antioxidants in the active form and better stability of olive oil [58-61]. Olive oil also contains some antioxidant micronutrients, namely polyphenols and squalene [58, 62-64]. The main MUFA in the human diet is oleic acid (C18:1n-9), which has one double bond. MUFA intake has been associated with a slight cardioprotective effect [65]. MUFAs are known to have a beneficial effect on the serum lipid profile and thus decrease the risk of CVD [66-68]. Furthermore, these fatty acids are stable in oxidative stress conditions and are less likely to react with reactive oxygen species (ROS) when compared with PUFA [58-59]. However, studies reporting associations between dietary intake of MUFAs and CHD risk have been inconclusive [69-71].

2.1.4. Polyunsaturated fat (PUFA)

PUFAs are naturally occurring endogenous substances, present in almost all tissues and are essential components of all mammalian cells. They are essential for survival and cannot be synthesized in the body. Hence, they have to be obtained in our diet and are therefore essential [54, 72]. There are two types of naturally occurring PUFAs in the body, the (n-6) PUFAs derived from linoleic acid (LA, C18:2) and the (n-3) PUFAs derived from α-linolenic acid (ALA, C18:3). They are categorized depending on the location of their first double bond: (n-3) PUFAs have their first double bond located at the third carbon molecule and (n-6) PUFAs at the sixth. Both of these two forms of PUFAs are metabolized by the same set of enzymes as their respective long-chain metabolites [73]. The differences between (n-3) and (n-6) PUFAs are shown in Table 1 below.

Vegetable oils are the predominant sources of alpha linolenic acid (ALA). ALA is found in legumes, flax seeds, walnuts, pinto beans, soybeans and spinach [74]. Dietary intake of ALA among Western adults is typically in the range of 0.5–2g/d [75]. The (n-6) PUFA is the main PUFA in most Western diets and is typically consumed in greater amounts than ALA [75, 76]. The evidence for a beneficial role of dietary (n-6) PUFAs is less convincing and for the purpose of this chapter we will focus on the (n-3) PUFA. The three main forms of (n-3) PUFAs are ALA, eicosapentaenoic acid (EPA, C20:5 n-3) and docosahexaenoic acid (DHA, C22:6 n-3) [77], with ALA being the simplest form. The (n-3) PUFAs are a family of biologically active fatty acids. The simplest member of this family, ALA, can be converted to the more biologically active and very long-chain (n-3) PUFAs; EPA and DHA. This process, as shown in Figure 1, occurs by a series of desaturation and elongation reactions, with stearidonic acid being an intermediate in the pathway [54, 75, 78].

Research has shown that long-chain (n-3) PUFAs protect against CVD [77, 79-82]. The cardioprotective effects of (n-3) PUFAs have long been recognized. Epidemiologic data suggest that (n-3) PUFAs derived from fish oil reduce CVD. Fish oil is a rich source of EPA (C20:5 n-3) and DHA (C22:6 n-3) (Table 1) [67, 83, 84]. The cardioprotective roles of these two forms of (n-3) PUFA are extensively reviewed by Bester and co-workers [48]. Fish oil may also reduce mortality after a cardiovascular incident, as it plays a role in reducing potentially fatal arrhythmias ([85-87]. There are several prospective studies relating the use of fish or the intake

of long-chain (n-3) PUFAs to lower risk of CVD [88, 89]. Long chain (n-3) PUFAs have several beneficial cardiovascular properties, including antiatherothrombotic, antiarrhythmic, anti-inflammatory, antihypertensive and triglyceride lowering [81, 90, 91]. In summary, studies investigating the dietary roles of fatty acids demonstrate that dietary supplementation with (n-3) PUFAs decreases cardiac deaths, nonfatal cardiovascular events and all-cause mortality. These benefits are most apparent in high-risk patients. (n-3) PUFA supplementation appears to confer additional benefits in patients eating a Mediterranean diet.

The original observation is from almost 57 years ago, when Hugh M. Sinclair [92] published his observations on the negative effects of essential fatty acid deficiency on CVD. He strengthened his hypothesis by noting the low mortality rate from CHD (coronary heart disease) in Greenland Eskimos, a population consuming a high fat diet, but rich in (n-3) PUFAs [92]. Clinical studies suggest that (n-3) PUFAs reduce mortality from coronary heart disease and the rate of sudden cardiac death [92-95]. Significant antiarrhythmic effects of (n-3) PUFAs were observed in some but not all human studies on atrial fibrillation [96, 97]. In addition, animal studies show strong antiarrhythmic effects of (n-3) PUFAs [98-102].

	(n-3) PUFA	(n-6) PUFA
Molecular structure	First double-bond on the third carbon counting from the methyl end (the "nth" carbon)	First double-bond on the sixth carbon counting from the methyl end (the "nth" carbon)
Types	α-Linolenic acid (ALA) [C18:3] Eicosapentaenoic acid (EPA) [C20:5] Docosahexaenoic acid (DHA) [C22:6]	Linoleic acids (LA) [C18:2] Arachidonic acid (AA) [C20:4]
Food sources	Flaxseed oil (ALA) Canola oil (ALA) Soybean oil (ALA) Oily fish (EPA/DHA) Fish oil capsules (EPA/DHA)	Corn oil(LA) Soybean oil (LA) Sunflower oil (LA) Poultry (AA) Meats (AA)

Table 1. Molecular structure, types and food sources of (n-3) and (n-6) PUFAs.

Long-chain (n-3) PUFAs are important constituents of all cell membranes and confer on membranes properties of fluidity and thus, determine and influence the behaviour of membrane-bound enzymes and receptors [103-107]. These PUFAs are found in abundance in the myocardium, retina, brain and spermatozoa, and are essential for the proper functioning of these tissues and growth, being important modulators of many physiological processes. The fact that these tissues have developed the cellular machinery to preferentially incorporate these minor dietary components into their membranes suggests that these PUFAs play a role in the proper function of the cell [108-110].

The fatty acid composition of myocardial membrane phospholipids, in particular, is sensitive to the type of fatty acid consumed in the diet. Studies show that indeed the myocardium and
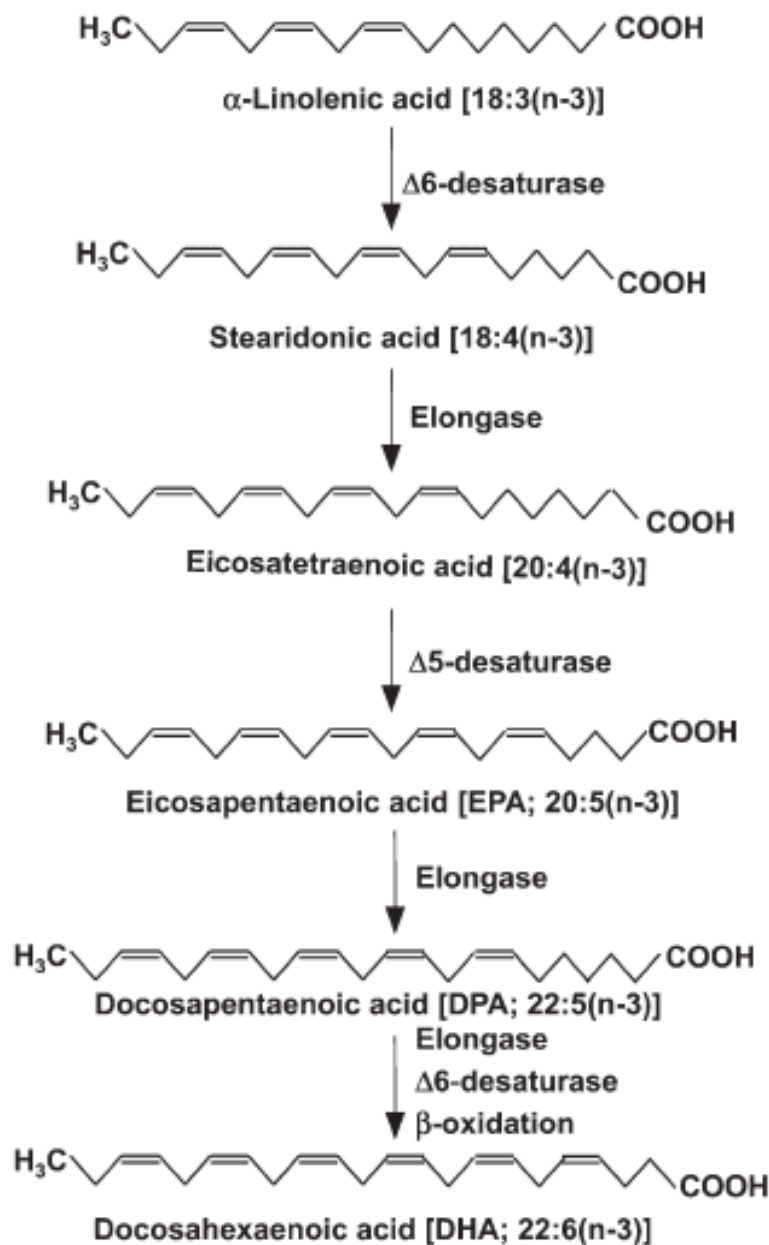
Figure 1. The biosynthesis of (n-3) PUFA.

myocardial membrane phospholipids are rich in (n-3) PUFAs after fish oil consumption [111, 112]. Diet-induced changes in the PUFA composition of a cell membrane have an impact on the cell's function, partly because these fatty acids represent a reservoir of molecules that perform important signalling roles within and between cells. In particular, dietary (n-3) PUFAs compete with dietary (n-6) PUFAs for incorporation into all cell membranes [113,114]. (n-3) PUFAs modulate the expression of adhesion proteins such as selectins [115] and exert an effect by modulating the intracellular signalling pathways associated with the control of transcription factors (e.g., nuclear factor-κB) and gene transcription [116,117]. Research has shown that enrichment of monocyte membranes with (n-3) PUFAs results in the synthesis and secretion

of reduced quantities of cytokines (e.g., tumour necrosis factor-α, interleukin-1β) that are involved in the amplification of the inflammatory response [117,118]. Therefore, at a cellular level, (n-3) PUFAs from fish oils can directly or indirectly modulate a number of cellular activities associated with inflammation.

2.1.5. Polyphenols

Polyphenols constitute one of the most numerous and ubiquitously distributed groups of plant secondary metabolites, with more than 8000 phenolic structures currently known. Natural polyphenols can range from simple molecules (phenolic acids, phenylpropanoids, and flavonoids) to highly polymerised compounds (lignins, melanins, tannins), with flavonoids representing the most common and widely distributed sub-group [119]. These secondary plant metabolites are known to have potential antioxidant activity and radical scavenging capacity [120-124]. Polyphenols are gaining increased importance due to their beneficial effects on health. Flavonoids are the most abundant polyphenols in our diets. They can be divided into several classes according to the degree of oxidation of the oxygen heterocycle: flavones, flavonols, isoflavones, anthocyanins, flavanols, proanthocyanidins and flavanones [125]. A complication of the epidemiological observations regarding members of the flavonoid family is that subtle differences in their chemical structures can translate into marked differences in their absorption, metabolism and bioactivities [126]. South African herbal teas, rooibos (*Aspalathus linearis*) and honeybush (*Cyclopia ssp.*) are currently gaining popularity worldwide [127, 128], owing to their anti-oxidant, anti-cancer and anti-mutagenic properties [129-131]. Rooibos is a herbal tea made from the leaves and stems of the indigenous South African plant, *Aspalathus linearis* (*Brum.f*) *Dahlg.* (*family Fabaceae; tribe Crotalarieae*) [132,133]. Research has demonstrated that this herbal tea is rich in flavonoids [127, 134]. Animal studies that have investigated the cardioprotective effects of natural or synthetic flavonoids have focused mainly on the acute pharmacological activity of these compounds. For example, *in vivo* studies using animal models have reported acute cardioprotection obtained from intravenous injections of natural or synthetic flavonoids [135,136].

2.1.6. Vitamin E

Natural vitamin E is composed of eight chemical compounds: α-, β-, γ- and δ-tocopherols and their corresponding tocotrienols. α-Tocopherol is the most active form of vitamin E *in vitro*. The tocopherols are saturated forms of vitamin E, whereas the tocotrienols are unsaturated and have an isoprenoid side chain. Tocopherols possess a chromanol ring and a 15-carbon tail. The presence of three *trans* double bonds in the tail distinguishes tocopherols from tocotrienols [137-139]. This may account for the differences in their efficacy and potency *in vitro* and *in vivo* [140,141].

Red palm oil (RPO) is a rich source of vitamin E. It contains 560–1000 parts per million of vitamin E, of which approximately 18–22% are tocopherols and 78–82% tocotrienols [142-144]. RPO has been shown to offer protection against I/R injury [42, 43, 47, 48] leading to a reduction in oxidative stress [145]. It has also been suggested that palm oil may have some anti-arrhythmogenic effects, which may reduce sudden death after ischaemic incidents [146].

Of all the vegetable oils, RPO has the highest content of tocotrienols with γ-tocotrienol the most abundant. This form of vitamin E has been demonstrated to reduce cholesterol production and platelet aggregation [147-151]. RPO may also exert a neutral or positive effect on the serum lipid profile through the effects of its fatty acid composition and tocotrienols [152-155]. Investigations into vitamin E showed that tocotrienols are more potent than tocopherols as antioxidants. The tocotrienols present in palm oil have been shown to offer protection from myocardial I/R injury in an isolated perfused rat heart model [156, 157]. Animal studies with tocopherols and tocotrienols that investigate these compounds' potential against chronic diseases are extensively reviewed by Aggarwal and co-workers [158]. These authors argue that the evidence overwhelmingly suggests that tocotrienols may be superior in their biological properties than tocopherols and that their anti-inflammatory and antioxidant activities could prevent CVD among other chronic diseases.

2.1.7. Carotenoids

Carotenoids are nature's most widespread pigments, well known for their orange-red to yellow colours, which they impart to many fruits and vegetables. These fat-soluble phytochemicals have also received substantial attention because of their provitamin A and antioxidant roles [159]. Carotenoids are polyenoic terpenoids with conjugated trans double bonds. They include carotenes (β-carotene and lycopene), which are polyene hydrocarbons and xanthophylls (lutein, zeaxanthin, capsanthin, canthaxanthin, astaxanthin and violaxanthin) that have oxygen in the form of hydroxy, oxo, or epoxy groups [160]. The majority of the 600 carotenoids found in nature are 40 carbons in length and may be pure hydrocarbons, called carotenes, or possess oxygenated functional groups, in which case they are called xanthophylls [161]. The long-chain conjugated polyene structure accounts for the ability of these compounds to absorb visible light, but also makes them quite susceptible to oxidation. This latter property is closely related to their ability to act as antioxidants [162].

The properties and therefore functions of a carotenoid molecule are primarily dependent upon its structure and hence its chemistry [163]. In particular, the conjugated C = C double bond system is associated with energy transfer reactions, such as those found in photosynthesis [164]. In human plasma and tissues, several carotenoids have been well characterized including cyclic (such as β-carotene and α-carotene) and acyclic carotenes (such as lycopene and phytoene), together with a number of xanthophylls (such as zeaxanthin, lutein and beta-cryptoxanthin), all of which can be directly derived from dietary sources [165]. Carotenoids have generated considerable interest as several studies have suggested an inverse association between the dietary intake of carotenoids and the risk for CVD [166, 167]. Conversely prooxidant roles of these phytochemicals have also been reported [168-170].

2.1.8. Possible mechanism(s) of action

As mentioned earlier, RPO supplementation does offer protection against myocardial I/R injury via several suggested mechanisms. Amongst the proposed mechanisms are the NO–cyclic GMP pathway, phosphorylation of mitogen-activated protein kinases and scavenging of deleterious reactive oxygen species by RPO [42, 43, 47, 48].

Investigations concerning (n-3) PUFAs show that these forms of essential fatty acids reduce the risk of sudden cardiac death as well as fatal and nonfatal myocardial infarction [171-173]. A number of mechanisms have been implicated in the protective effects of (n-3) PUFAs [174, 175]. The (n-3) PUFAs have been demonstrated as altering the transcription of specific genes. These effects are mediated by a variety of mechanisms that involve indirect (i.e., by eicosanoids, hormones) and direct nuclear effects on genes. The PUFAs (i.e., both (n-3) and (n-6) PUFAs) modulate the expression of genes involved in lipogenesis, glycolysis, production of glucose transporters, inflammatory mediators, early response genes and genes for cell adhesion molecules [176, 177].

The primary source of MUFA that lowers cholesterol levels is olive oil [178, 179]. It is evident that olive oil, due to its micronutrient content and fatty acid composition, can play a vital role in maintaining beneficial serum lipid profiles. Together with its ability to reduce systemic oxidative stress, blood pressure and inflammation, it has become an appropriate dietary supplement for lowering the risk of CHD.

2.2. Composition and health benefits of nuts

Nuts are highly nutritious and of prime importance for people in several regions in Asia and Africa. Most nuts contain a great deal of fat (e.g., pecan 70%, macadamia nut 66%, Brazil nut 65%, walnut 60%, almonds 55% and peanut butter 55%). Most have a good protein content (in the 10–30% range) and only a few have a very high starch content [180]. Many nuts have also been identified as especially rich in antioxidants [181, 182]. Nuts therefore constitute one of the most nutritionally concentrated kinds of food available. Most nuts, left in their shell, have a remarkably long shelf life and can conveniently be stored for winter use [183]. Nuts are foods rich in fat, ranging from 46% in cashews and pistachios to 76% in macadamia nuts and provide 20–30 kJ/g per nut. Despite their high fat content, they are not harmful because they contain a low proportion (4–16%) of saturated fatty acids. Nearly one half of the fat content of nuts consists of unsaturated fatty acids, including both mono- (oleic acid) and poly- (linoleic and α-linolenic acid) unsaturated fatty acids (MUFA and PUFA respectively). The fatty fraction of nuts also contains plant sterols with anti-oxidants [184] and cholesterol-lowering effects [185]. Nuts are also rich sources of other bioactive macronutrients, such as protein (25% of energy) and dietary fibre, which ranges from 4 to 11g/100 g and in standard servings provide 5–10% of daily fibre requirements. They also contain significant micronutrients (Table 2), among them folate [185] antioxidant vitamins (e.g., tocopherols) and phenolic compounds [183].

By virtue of their unique composition, nuts are likely to benefit modern cardiovascular risk biomarkers, such as LDL oxidizability, soluble inflammatory molecules and endothelial dysfunction. The complex pathophysiology of atherosclerotic disease has evolved beyond the accumulation of cholesterol in the arterial wall. A series of circulating, functional, structural and genomic biological markers that reflect arterial vulnerability have been proposed as potential novel risk factors for the development of CVD (Vasan, 2006). Among them, biomarkers for oxidation [186], inflammation [187] and endothelial dysfunction [188] have received increasing attention.

Average nutrient composition of nuts (per 100 g)[1]

Nuts	Energy	Total fat	SFA	MUFA	PUFA	Plant sterols	Total protein	Arginine	Fiber	Folate	α-Tocopherol	Calcium	Magnesium	Potassium
	kJ	g	g	g	g	mg	g	g	g	µg	mg	mg	mg	mg
Almonds	2418	50.6	3.9	32.2	12.2	120	21.3	2.47	8.8	29	25.9	248	275	728
Brazil nuts	2743	66.4	15.1	24.5	20.6	NR	14.3	2.15	8.5	22	5.7	160	376	659
Cashews	2314	46.4	9.2	27.3	7.8	158	18.2	2.12	5.9	25	0.9	37	292	660
Hazelnuts	2629	60.8	4.5	45.7	7.9	96	15.0	2.21	10.4	113	15.0	114	163	680
Macadamias	3004	75.8	12.1	58.9	1.5	116	7.9	1.40	6.0	11	0.5	85	130	368
Peanuts (dry roasted)	2448	49.7	6.9	24.6	15.7	NR	23.7	3.1	8.0	145	6.9	54	176	658
Pecans	2889	72.0	6.2	40.8	21.6	102	9.2	1.18	8.4	22	1.4	70	121	410
Pine nuts (dried)	2816	68.4	4.9	18.8	34.1	141	13.7	2.41	3.7	34	9.3	16	251	597
Pistachios	2332	44.4	5.4	23.3	13.5	214	20.6	2.03	9.0	51	2.3	107	121	1025
Walnuts	2738	65.2	6.1	8.9	47.2	72	15.2	2.28	6.4	98	0.7	98	158	441

Table 2. Composition of Nuts (data from the US department of agriculture nutrient database)

Studies had shown that whole, unprocessed and unpeeled nuts have a unique composition that consists of important macro- and micronutrients, which give nuts their multiple beneficial effects on cardiovascular outcomes [189-192]. Most nut constituents have shown beneficial effects when clinically tested, in isolation or as part of enriched foods, for effects on diverse cardiovascular outcomes, including novel risk markers [189-192].

2.2.1. Antioxidant effects

Nuts are important sources of tocopherols and phenolic antioxidants, which protect against LDL oxidation [183]. Walnuts have been shown to contain substantial amounts of melatonin, which contributed to a significant antioxidant effect in an experimental rat model [193]. In addition, a substantial fraction of nut fat comes from MUFAs, which are not susceptible to oxidation. The PUFAs are contained mainly in walnuts and are more susceptible to oxidation. However, nuts are a rich source of many antioxidants, which protect the PUFA *in vivo* against oxidative modification [194].

2.2.2. Anti-inflammatory effects

Plasma high-sensitivity CRP, an accepted measure for systemic low-grade inflammation, was a secondary outcome in several controlled nut feeding trials conducted in hypercholesterole-mic subjects with almonds [195-198] or walnuts [197, 199]. Some of them have demonstrated a CRP-lowering effect [196, 197, 198]. Zhao et al., who used walnuts and walnut oil to enrich the diet in PUFA and especially ALA, showed a decrease in inflammatory markers [197] and proinflammatory cytokine production by mononuclear cells [197].

2.2.3. Effects on endothelial function

Endothelial dysfunction is a critical event in atherogenesis and is implicated both in early disease and in advanced atherosclerosis [201]. Short-term feeding studies have shown consistently that diets rich in saturated fatty acids impair endothelial function [181, 202, 203] and that even a single fatty meal rich in saturated fatty acids is followed by transient endothelial dysfunction [204, 205]. These detrimental effects can be counteracted by the

administration of PUFA and other nutrients contained in nuts, such as antioxidant vitamins and arginine [179]. Another feeding trial showed that, compared with an isoenergetic Mediterranean diet with similar saturated fatty acid content, a walnut diet attenuated the endothelial dysfunction associated with hypercholesterolemia [199]. Moreover, changes in circulating levels of cellular adhesion molecules critical to leukocyte recruitment on the arterial wall also reflect endothelial dysfunction [201]. Several studies have shown that diets enriched with ALA from walnuts [197, 199, 206] reduce endothelial activation as assessed by decreased plasma cellular adhesion molecules. Walnut feeding also reduced the expression of endothelin-1, a potent endothelial activator in an animal model of accelerated atherosclerosis [207].

2.2.4. Effects on body weight changes

As the interest in incorporating nuts into the diet grows, it is important that consumers understand how to include them in a healthy diet without promoting weight gain. They are high-fat, energy dense foods and are therefore a potential threat for contributing to positive energy balance. Numerous epidemiological and clinical studies have shown that nuts are not associated with higher body weight [208, 209] or weight gain [210-215]. This could be attributed along with other potential mechanisms for the high satiety properties of nuts [216]. The enhanced satiety, which is also achieved via other mechanisms such as the decreased eating rate [217], leads to reduced energy consumption and therefore a decreased risk of weight gain and obesity.

Blomhoff et al. [190] argued that the inverse association between nut intake and cardiovascular and coronary heart diseases in epidemiological studies may, or may not, be associated with antioxidants. According to these authors, epidemiologic studies are not ideally suited for studying the role of specific nuts or biological mechanisms. Nevertheless, they are in agreement with findings supporting the theory that a complex and rich mix of nut constituents is able to offer protection against CVD and perhaps other chronic diseases [183].

2.2.5. Possible mechanism(s) of action

Epidemiologic and clinical trial evidence has demonstrated the beneficial effect of nut consumption on coronary heart disease and its associated risk factors. The cardioprotective properties of nuts, due partially to their favourable lipid fatty acid profile (rich in unsaturated fatty acids), exceed the LDL-C lowering. Nuts, especially walnuts, contain (n-3) PUFAs, which have been shown to have a favourable impact on multiple factors related to CVD, such as inflammation, platelet function, arrhythmias, hypertriglyceridemia and nitric oxide-induced endothelial relaxation [218]. Nuts are also excellent sources of other bioactive compounds such as vegetable protein, dietary fibre, potassium, calcium, magnesium, tocopherols, phytosterols, phenolic compounds, resveratrol and arginine [179]. This unique nutrient composition explains the benefits of nut consumption for the prevention of CVD through mechanisms of oxidation, inflammation and vascular reactivity.

3. Conclusions and future directions

Investigation of the mechanisms underlying CVD showed that the disease has a complex cause beyond the accumulation of cholesterol on the arterial wall, with enhanced oxidative stress and a prominent inflammatory response. Diet has been shown to be associated with cardiovascular events. PUFAs are essential in our diet because we cannot synthesize them. They are also essential nutrients for optimal health of the cardiovascular, nervous and undoubtedly other organ systems. Dietary (n-3) PUFAs are incorporated into the cellular membranes of all tissues. The extent of incorporation into tissue membranes is dependent on dietary intake. The enrichment of membranes with (n-3) PUFAs can modulate cellular signalling events, membrane protein function and gene expression.

Interest in the possible health benefits of flavonoids has increased owing to their potent antioxidant and free-radical scavenging activities observed *in vitro*. There is growing evidence from human feeding studies that the absorption and bioavailability of specific flavonoids is much higher than originally believed. However, epidemiologic studies exploring the role of flavonoids in human health have been inconclusive. Some studies support a protective effect of flavonoid consumption in CVD and cancer; other studies demonstrate no effect and a few studies suggest potential harm. More recently, results from human studies provide evidence that rooibos can offer protection against oxidative stress conditions such as CVD [131,219]. In a study by Pantsi et al., the beneficial effects of dietary rooibos flavonoids were observed *ex vivo* in isolated perfused rat hearts. Epidemiological studies suggest that the beneficial cardiovascular health effects of diets rich in fruit and vegetables are in part mediated by their flavonoid content, with particular benefits provided by one member of this family, the flavonols [49].

Polyphenols are abundant micronutrients in our diet and evidence for their role in the prevention of degenerative diseases is emerging. Bioavailability differs greatly from one polyphenol to another, so the most abundant polyphenols in our diet are not necessarily those leading to the highest concentrations of active metabolites in target tissues. Because there are many biological activities attributed to the flavonoids, some of which could be beneficial or detrimental depending on specific circumstances, further studies in both the laboratory and with populations are warranted.

However, the fatty acid components of nuts may differently influence oxidation processes and this needs to be considered for the synergy or opposition to the effects of constituent antioxidants. There is growing evidence that dietary polyphenols in nuts, tea and wine may have anti-inflammatory effects, mediated by both their antioxidant action and modulation of signal transduction pathways, such as the nuclear transcription factor kB, with ensuing down-regulation of inflammatory genes in endothelial cells and macrophages [220]. The increased diversity and availability of sources of dietary fatty acids will likely allow the continued expansion of food products fortified with these fatty acids, a trend that may result in the attainment of the recommended dietary intake of these nutrients.

Future studies in oils should be carried out in order to elucidate the effects of oils in various models in which effects remain unknown. Little is known about the effects of nuts on a diseased

heart. Studies should be performed to test whether nuts may offer protection against the severity or progression of various models of CVD.

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