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Review Article

Nutraceuticals and Atherothrombosis: A Glance to Human Trials

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Abstract

The leading causes of death worldwide are ischaemic heart disease and stroke. These Cardiovascular Diseases (CVDs) are two of the main clinical manifestations of atherothrombosis. Above all, the major causes of this complex condition include genetic susceptibility along with lifestyle habits or behavioral risk factors such as smoking, physical inactivity, alcohol abuse, and unhealthy diets. The most important way to prevent atherothrombotic events is through lifestyle optimization. In particular, nutritional intervention plays a key role in the treatment and prevention of atherothrombosis, with specific dietary patterns as potential modulators of cardiovascular health. Nutraceuticals are substances derived from food and offer health benefits along with their nutritional value and could become promising agents in the prevention and treatment of CVDs, particularly for individuals or populations with low adherence to certain dietary patterns. However, for most nutraceuticals, the evidence for their use in cardiovascular health is limited and requires further attention. This review will summarize some nutraceuticals with strong evidence from large sample size randomized controlled trials for the primary or secondary prevention of CVDs.

Keywords: Nutraceuticals; Atherothrombosis; Cardiovascular diseases; Nutrition; Omega-3; Olive oil

Abbreviations

AHA: American Heart Association; ASCEND: The Study of Cardiovascular Events in Diabetes; CARDIOPREV: Coronary Diet Intervention with Olive Oil and Cardiovascular Prevention Study; CVDs: Cardiovascular Diseases; DHA: Docosahexaenoic Acid; EPA: Eicosapentaenoic Acid; EUROLIVE: Effect of Olive Oil Consumption on Oxidative Damage in European Populations; EVOO: Extra-virgin Olive Oil; HDL: High Density Lipoprotein; HT: Hydroxytyrosol; iEPA: icosapent ethyl; MACE: Major Cardiovascular Events; PREDIMED: Prevención con Dieta Mediterránea; REDUCE-IT: Reduced of Cardiovascular Events with Icosapent Ethyl-Intervention Trial; RCT: Randomized Controlled Trial; PUFA: Polyunsaturated Fatty Acids; STRENGHT: The Statin Residual Risk Reduction with Epanova in High CV Risk Patients With Hypertriglyceridemia Trial; VITAL: Vitamin D and Omega-3 Trial.

Introduction

Cardiovascular diseases represent the leading causes of death worldwide, being the first two places occupied by ischaemic heart disease and stroke [1]. These conditions relate to genetic predisposition, behavioral factors (i.e., alcohol consumption, and tobacco use), and lifestyle (i.e., inadequate dietary habits, and low physical activity) [2]. CVDs are clinical manifestations of atherothrombosis, a generalized and progressive process that affects multiple arterial beds, characterized by a thrombus formation over an unstable atherosclerotic plaque [3]. The pathophysiology is complex and involves processes such as endothelial cell activation, abnormal lipid metabolism, low-grade inflammation, oxidative stress, leukocyte activation, and further platelet aggregation [3]. Healthy dietary patterns and food components can impact most of these factors; the current guidelines recommend them as adjuvant therapy for clinical manifestations of atherothrombosis [4].

In particular, nutritional intervention plays a pivotal role in the prevention of atherothrombotic events. Thus, a correct nutrient distribution along with healthy food choices may contribute to the stabilization of vulnerable plaques and further prevention of thrombus formation [5]. In this regard, the Mediterranean diet is recognized as a healthy dietary pattern since is low in saturated fatty acids, and high in mono and polyunsaturated fatty acids, and polyphenols. Hence, these specific features make the Mediterranean diets effective nutritional interventions for atherothrombotic events (e.g., acute myocardial infarction and stroke) [6,7]. However, low income and education level could decrease the adherence to a healthy dietary pattern, which becomes a problem for a significant portion of contemporary societies [8].

The study of nutraceuticals (i.e., biologically active products derived from food sources with health benefits besides their nutritional value), has focused on the components of healthy dietary patterns [9,10]. The novelty of nutraceuticals relies upon the simplicity of the intervention and their impact on physiological functions (e.g., lipid metabolism, and oxidative stress). Together this may contribute to the treatment and prevention of atherothrombosis. Though there are several nutraceuticals studied, the major problem remains in the lack of large clinical trials and cohort studies to address their effectiveness in this topic [10].

This review aims to highlight the nutraceuticals with evidence from large sample size Randomized Controlled Trials (RCTs) found in the literature, for the primary or secondary prevention of CVDs. In order to do this and after an extended search for RCTs of

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nutraceuticals studied in cardiovascular disease, atherosclerosis, or atherothrombosis, we found major discrepancies in the literature. This may be due to different interventional approaches, sample sizes, dose of the nutraceutical, and diversity of the studied groups (e.g., healthy, obese, diabetic, and high risk for CVD individuals). However, this review will approach two nutraceuticals, which are key components of the Mediterranean diet (i.e., omega-3 fatty acids, and olive oil derivatives). Since they have recent data from large RCT and cohort studies of relevant outcomes (Table 1). Nonetheless much more nutraceuticals with substantial evidence have been thoroughly described elsewhere [9,10].

Omega-3 Fatty Acids

These Polyunsaturated Fatty Acids (PUFAs) have proved cardioprotective effects in several cellular and animal models. The human inability to synthesize them besides their moderate amount in food reinforces their use as nutraceuticals. Some of the most studied PUFAs regarding atherothrombosis prevention are omega-3 fatty acids, especially Eicosapentaenoic (EPA) and Docosahexaenoic (DHA) acids. Though, EPA gained further attention since appears to be responsible for reduction of cytokine expression, improvement of endothelial cell function, decrease in triglycerides synthesis, and inhibition of blood platelet aggregation on *in vitro* and *in vivo* models [11]. All the above is in the pathophysiology of atherothrombosis [12]. The American Heart Association (AHA) has recommended the use of 460mg of EPA and 380mg of DHA per day. However, its relevance in primary and secondary prevention of CVDs from clinical trials is still debatable [9].

Regarding primary prevention of CVDs, two large RCTs concluded that supplementation with omega-3 fatty acids does not result in a lower incidence of Major Cardiovascular Events (MACE). The first is the vitamin D and omega-3 trial (VITAL), a placebo-controlled, two-by-two factorial trial (n=25,871). The VITAL study assessed the effect of daily supplementation in healthy individuals with either vitamin D3 or omega-3 fatty acids (DHA: 380mg/ EPA: 460mg). With a MACE established as primary endpoint (i.e., myocardial infarction, stroke, or cardiovascular death). After a 5-year follow-up, they concluded that omega-3 fatty acids supplementation does not offer a significant reduction in MACE. The Study of Cardiovascular Events in Diabetes (ASCEND) trial (n=15,480) evaluated omega-3 fatty acids supplementation (DHA: 380mg/EPA: 460mg) versus olive oil as a placebo, in diabetic patients. Their primary outcome was a first vascular event (i.e., stroke, nonfatal myocardial infarction, transient ischemic attack, or vascular death). Similar to VITAL, but after 7 years of follow-up, they reported no significant differences in the risk of a MACE between omega-3 fatty acid or placebo groups [13].

The discrepancies arrived with the study Reduced of Cardiovascular Events with Icosapent Ethyl–Intervention Trial (REDUCE-IT, n=8179). This RCT assessed the supplementation of 4g a day with a highly purified EPA (icosapent ethyl, iEPA) *vs.* mineral oil (as a placebo). And included individuals with CVD, diabetes, or other risk factors, and treated with statins. Their established primary outcome was a composite of cardiovascular events (i.e., CV death, stroke, myocardial infarction, stroke, coronary revascularization, and unstable angina). After a 5-year follow-up, the conclusion was that supplementation with iEPA promotes a reduction in first cardiovascular events. Though dosage could be the primary reason for these positive results, a further RCT study discards this notion. In this respect, the Statin residual risk reduction with epanova in high CV risk patients with hypertriglyceridemia trial (STRENGHT,

Table 1: Summary of major nutraceuticals used in randomized controlled trials on cardiovascular health.

Nutraceutical	RCT	Sample Size	Duration/Participants	Intervention	Major Findings	Ref
Omega-3	VITAL	25,871	5-years, Healthy adults	EPA (460mg/d) and DHA (380mg/d) or placebo	No reduction in the rates of MACE	[15]
	ASCEND	15,480	7-years. Patients with diabetes but without evidence of CVD	EPA (460mg/d) and DHA (380mg/d) or placebo	No reduction rates of nonfatal serious adverse events	[13]
	REDUCE-IT	19,212	5-years. Patients with established CVD, diabetes, and/or risk factors, with statin therapy	4g/d of Icosapent ethyl (a highly purified EPA) or placebo	A 25% reduction in primary cardiovascular outcome, and 26% reduction in the secondary endpoint	[25]
	STRENGHT	13,078	2-years. Adults with high CVD risk with statin therapy, hypertriglyceridemia, and low levels of HDL-cholesterol	4g/d Epanova (each gram composed by 550mg of EPA, and 200mg of DHA) or placebo	No significant difference in a composite outcome of MACE	[14]
Olive oil	CARDIOPREV	805	1-year. Patients with previous coronary heart disease but the last coronary event before six months of enrollment	Mediterranean diet rich in olive oil compared with a low-fat diet.	Better modulation of endothelial function by the Mediterranean diet rich in olive oil than with low-fat diet.	[17]
	PREDIMED	7447	4.8-years. Adults with high cardiovascular risk.	Three groups • Mediterranean diet plus 50ml/d of EVOO. • Mediterranean diet plus 30g/d of nuts. • Low-fat diet	A lower incidence of MACE among those supplemented with EVOO and nuts in a Mediterranean diet.	[18]
	EUROLIVE	200	3-weeks. Healthy male volunteers	Three groups supplemented with 25ml/d of olive oils of different phenolic content: low (2.5mg), medium (164mg), and high (366mg)	Increase in serum HDL-cholesterol levels and decreased in markers of oxidative stress markers in line with phenolic content.	[22]

ASCEND: The Study of Cardiovascular Events in Diabetes; CARDIOPREV: Coronary Diet Intervention with Olive Oil and Cardiovascular Prevention Study; EPA: Eicosapent Ethyl Acid; DHA: Docosahexaenoic Acid; EUROLIVE: Effect of Olive Oil Consumption on Oxidative Damage in European Populations; EVOO: Extra-Virgin Olive Oil; HDL: High Density Lipoprotein; PREDIMED: Prevención con Dieta Mediterránea; REDUCE-IT: Reduced of Cardiovascular Events with Icosapent Ethyl-Intervention Trial; STRENGHT: The Statin Residual Risk Reduction with Epanova in High CV Risk Patients With Hypertriglyceridemia Trial; VITAL: Vitamin D and Omega-3 Trial.

n=13,078) showed opposite results. This RCT assessed 4-gram daily supplementation with Epanova (each gram composed by 550mg of EPA, and 200mg of DHA). However, the study was interrupted early owing to perceived futility [14]. Hence, instead of dosage, the composition of omega-3 fatty acids, preferring EPA to DHA, is a key feature in the protection for MACE (33095318). According to these results, the current guidelines of the European Society of Cardiology recommend icosapent ethyl for patients with high triglyceride levels in statin treatment [15].

Olive Oil Derivatives

Nutraceuticals can be part of functional foods such as olive oil, a key component of a Mediterranean diet, and might relate to the evidence of this dietary pattern in cardiovascular health. The composition of olive oil includes a saponifiable fraction (98-99 %) represented by oleic acid, and of an unsaponifiable fraction (1-2 %) composed for tocopherols, and polyphenols (e.g., tyrosol, oleuropein, and hydroxytyrosol) [16].

As compared to omega-3 fatty acids, the evidence for olive oil is still scarce and questionable about the effect of each fraction on cardiovascular health. However, two relevant RCTs approached the effect of olive oil on this topic. The sub-study of the coronary diet intervention with olive oil and cardiovascular prevention study (CARDIOPREV) analyzed the effect of a diet rich in olive oil *vs*. a low-fat diet (n=805). This trial included patients with previous coronary heart disease but no coronary event in the previous six months before enrollment. Results showed that a diet rich in olive oil associate with a better endothelial function (assessed by flow-mediated dilation of the brachial artery) in coronary heart disease patients after 1-year follow-up [17]. Likewise, in the Prevención con dieta mediterránea (PREDIMED) trial, assessed the effect of a Mediterranean diet supplemented with Extra-Virgin Olive Oil (EVOO) (50ml/day) or nuts (30g/day), *vs*. a low-fat diet (n=7447) in adults at high cardiovascular risk. The supplemented groups exhibited a decreased incidence of cardiovascular events (i.e., myocardial infarction, stroke, or cardiovascular death) after a 4.8-year follow-up [18]. Although similar results were found within the nuts group, Alpha-linoleic acid (a plant-derived omega-3 fatty acid) could explain similar effects since it may also exert cardioprotective effects [19].

Regarding the phenolic components of the extra-virgin olive oil (i.e., tyrosol, hydroxytyrosol, and oleuropein), they have several biological effects, including antioxidant activity and anti-inflammatory properties [20]. The polyphenol Hydroxytyrosol (HT) has been the most widely studied. Although it has a short lifespan, HT incorporates into plasma HDL-cholesterol and might work in cardiovascular health. Clinical evidence from HT derived from EVOO is inconclusive, as evidenced by a recent meta-analysis [21]. However, a small clinical trial (n=40) of three weeks intervention suggests that administration of HT (15mg/day) modulates the antioxidant profile and the expression of genes related to oxidative stress [22]. Likewise, a larger RCT performed in healthy volunteers (n=200) assessed supplementation with olive oil of three different polyphenol content (i.e., low, medium, and high). Results showed a linear increase in HDL-cholesterol, and reduction in oxidative stress markers, with the phenolic content of the olive oil. The authors concluded that olive oil is more than monounsaturated fat [23]. However, these results are not enough evidence to use nor recommend polyphenolic-enriched olive oil and further RCTs remained to be performed [24].

Conclusion

Nutraceuticals are promising agents as adjuvants in the prevention and treatment of CVDs. Omega-3 fatty acid supplementation present a challenge since despite being the ones with stronger and considerable evidence, the content and dosage is still uncertain. Concerning olive oil derivatives and their value as potential agents for cardiovascular health, there is an imperative demand for a deeper appraisal of them in large trials. Overall, RCTs require further consistency regarding sample size, composition, length, and dosage of the agent in order to reduce disparities in nutraceutical effectiveness. In brief, dietary patterns supplemented with either olive oil and in specific omega-3 fatty acids would demand absolute critical thinking of clinicians on dosage and composition when recommend their use.

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