

The Benefits of Selected Nutritional Compounds Towards Atherosclerosis Management

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Abstract: Globally, the prevalence of obesity, type 2 diabetes, and metabolic syndrome is steadily rising, potentially giving rise to the most extensive non-communicable health crisis ever recorded blocking the flow are able to break and cause a blood clot. The possible consequence is a significant increase in atherosclerotic cardiovascular disease rate. The atherosclerotic cardiovascular disease largely depends on modifiable factors, however, even though there are significant efforts to manage traditional risk factors, a significant residual risk remains, which varies depending on studies and statistical analysis methods. Currently, lifestyle recommendations have not succeeded in having a proper impact on the burden of the double epidemic of metabolic diseases and atherosclerotic cardiovascular disease. Increasing healthcare costs indicate the need for fresh strategies that are able to improve long-term commitment in the future. In this review, we summarized data on the dietary impact on atherosclerosis, paying special attention to the nutrients that have the potential antiatherosclerotic activity. Today, it is obvious that maintaining a healthy lifestyle is one of the main components of the prevention and treatment of cardiovascular diseases. Diet is one of the most important components of a healthy lifestyle. Unfortunately, there is no uniquely ideal power scheme. Although the beneficial effects of a number of nutritional compounds and their mechanisms have been described, the development of an ideal diet for each individual subject is a challenge for future research.

Keywords: Atherosclerosis, Cardiovascular Disease, Nutrition, Diet

Introduction

A distinctive feature of atherosclerosis development is the deposition of fatty and/or fibrous material in the intima. Originating from the Greek language, atherosclerosis literally means “porridge” or “grain” due to the fact that lipid material, which is located in the core of an ordinary atheroma (or atherosclerotic plaque) looks similar. Over time, the atherosclerotic plaque is able to become more fibrous and store the calcium mineral. Developing atherosclerotic plaques can enter the lumen of the arteries, thereby blocking blood flow and resulting in tissue ischemia (Linton *et al.*, 2019; Summerhill *et al.*, 2019).

Those atheromas that do not create an obstacle blocking the flow are able to break and cause a blood clot

formation, which, in turn, is able to block the lumen, providing a more acute path to ischemia. Nowadays, the most frequent cause of vascular diseases globally is atherosclerotic Cardiovascular Disease (CVD). When CVD affects the heart's own blood circulation, it is able to result in acute coronary syndromes such as Myocardial Infarction (MI) or chronic conditions such as stable angina (chest pain or discomfort due to insufficient perfusion of the heart muscle) (Chiu and Chien, 2011). Atherosclerosis can lead to a variety of ischemic strokes and transient ischemic attacks of the brain. Thus, aneurysms are formed, including those located in the abdominal aorta. When it affects peripheral arteries, it can lead to intermittent claudication, ulceration, and

gangrene, which makes the viability of the limbs extremely vulnerable (Zemaitis *et al.*, 2022).

Atherosclerosis is a key cause of death worldwide. In recent years, great progress has been made in understanding the pathogenesis and treatment strategy development. Sadly, despite significant advances in prevention, a huge number of people outside hospitals continue to die due to acute complications. Nevertheless, when patients with acute atherosclerosis are hospitalized, with the current interventions and treatment strategies, the lives of these patients are usually successfully saved (Low Wang *et al.*, 2016). This advance in cardiovascular medicine is an excellent example of how the clinical application of scientific discoveries can benefit patients. However, in order to achieve a more effective and fair application of what is already known in practice, much remains to be done. It is also necessary to continue trying to end the global epidemic of cardiovascular diseases. Most of the patients survive acute coronary syndromes, however, they may still have impaired cardiac function, which contributes to heart failure (Mensah *et al.*, 2017).

Among the potential management options, a significant role is played by lifestyle corrections. A big part of such corrections corresponds to the diet. The purpose of our review was to examine the potential beneficial effect of various nutrients for atherosclerosis. The main method of our study was the literature search. To select initial papers, we searched the PubMed database by "nutrients" and "atherosclerosis" keywords among publications made in 2018-2023. According to these initial findings, we selected vitamins, omega-3, omega-6, carotenoids, stilbenes, Coenzyme Q10, flavonoids, and phytosterols to be overviewed in the context of our review.

Diet as a Risk Factor

When it comes to both quantity and quality, inadequate nutrition stands out as a primary contributor to disabilities and deaths worldwide. Throughout recent decades, suggestions for a healthy diet have primarily centered on calorie and nutrient aspects. An essential objective has been to restrict the consumption of certain dietary fats, particularly saturated fats. Nevertheless, there is a lack of evidence showing that these efforts have substantially alleviated the burden of cardiometabolic diseases. The primary flaw in the calorie and nutrient approach lies in its failure to consider the intricate and weight-independent impact of food composition and diet on metabolic and hormonal reactions tied to feelings of fullness and other intermediary pathways relevant to cardiovascular health and overall well-being. These pathways can involve factors such as the gut microbiome. Adding to this complexity is the hesitation to rely on potentially error-prone methods in nutritional epidemiology when formulating dietary guidelines

(Branca *et al.*, 2019). Assessment methods that are based on memory (for example, questionnaires about the frequency of meals) are able to provide physiologically implausible data (i.e., incompatible with viability) (Naska *et al.*, 2017).

Food-Versus Nutrient-Based Recommendations

Evaluation of food's effect on health by its individual nutrients without taking into account the food matrix does not provide significant information. The data obtained at clinical endpoints gives reliable support for the benefits of food-based recommendations without specific calorie indications in contrast to recommendations based on nutrients and calories (Fardet and Rock, 2018). The results confirming this concept were obtained due to 2 major studies of dietary intervention with endpoints of the cardiovascular system (Ravera *et al.*, 2016).

The PREDIMED study demonstrated that among participants at high risk of CVD who followed a Mediterranean-style diet without calorie restriction, supplemented with four tablespoons of extra virgin olive oil or 30 g of nuts per day for 4.9 years, inflammation decreased by 31% and the frequency of serious cardiovascular events decreased by 28% (Ros, 2017). It should be noted that these effects did not depend on both body weight and lipid-lowering. This is very different from the Women's Health Initiative (WHI), the largest dietary randomized controlled trial ever conducted. In WHI, a low-fat diet with clear calorie recommendations did not achieve a significant reduction in the endpoints of CVD after 8 years, despite the significant reduction in total fat intake achieved (from 37.8-28.8%) (Prentice *et al.*, 2017).

Carbohydrate Restriction/Nutritional Ketosis

Insulin resistance replaces metabolic responses to dietary signals. Despite the considerable and not yet fully understood complexity at the cellular and molecular level, insulin resistance is clinically manifested in the form of intolerance to dietary carbohydrates; glycogen synthesis is disrupted and dietary carbohydrates are increasingly directed to de novo lipogenesis in the liver (Yazıcı and Sezer, 2017). Theoretically, these findings hold important implications for dietary advice concerning MetS and T2DM. They also offer a reasonable rationale for the observed evidence backing the adoption of dietary carbohydrate reduction and (intermittent) calorie restriction in individuals with dyslipidemia and insulin resistance. These dietary strategies showcase beneficial metabolic alterations even without a significant decrease in body weight (Hoyas and Leon-Sanz, 2019).

Interestingly, limiting carbohydrate intake is not a new idea: Before the discovery of insulin, it was effectively used in the treatment of diabetes mellitus. Discovered in 1923, insulin made it possible to control the acute symptoms of diabetes even with diets high in

carbohydrates and this powerful therapy was almost completely forgotten (Hallberg *et al.*, 2019).

The identification of cellular and metabolic reactions to carbohydrate restriction reignited scientific curiosity about these dietary approaches. In cases of insulin-resistant traits, adopting a highly reduced carbohydrate diet that induces nutritional ketosis has been shown to lessen systemic inflammation and lower the majority of biomarkers associated with the risk of atherosclerotic cardiovascular disease (Mattson *et al.*, 2017).

Reducing inflammation mechanistically ties to β -Hydroxybutyrate (BHB), a ketone body. BHB, crucially in nutritional ketosis, acts as a metabolic agent and signaling molecule (Newman and Verdin, 2017). BHB inhibits NLRP3 inflammasome, an innate immune sensor, curbing downstream interleukin 1 beta (IL-1 β), a key CVD risk factor. Notably, the CANTOS study showed that IL-1 β suppression lowered cardiovascular events (Grebe *et al.*, 2018; Lutgens *et al.*, 2019). BHB also suppresses histone deacetylase class 1 (HDACs), affecting gene expression, and encompassing pathways in longevity and cardiometabolic health (McIntyre *et al.*, 2019). BHB's impact extends to vascular aging and a healthy microbiome (Dowis and Banga, 2021).

Caloric Restriction

Calorie restriction refers to dietary interventions that involve reducing energy consumption without malnutrition and while it consistently extends healthy life expectancy in various species, achieving long-term stability in humans remains a significant challenge for most individuals.

The promising aspect is that intermittent fasting regimes trigger comparable cellular and metabolic adaptations to chronic calorie restriction, providing encouragement. Time-limited food intake has shown associations with improved cardiometabolic health in animals and among humans as well (Hofer *et al.*, 2022).

Episodes of intermittent negative energy balance trigger metabolic adjustments, transitioning from producing and storing fats to releasing them as free fatty acids and fatty acid-derived ketones. This shift correlates with enhanced surrogate indicators of cardiometabolic well-being, encompassing weight loss and favorable impacts on body composition, like visceral fat reduction and muscle mass preservation (Lechner *et al.*, 2020).

After these changes, there's a rise in circulating ketones and a decrease in inflammatory cytokines, fatty acids, amino acids, glucose, and insulin levels. This leads to improved insulin sensitivity and lipoprotein metabolism. For those with insulin resistance, eating all daily calories in the morning instead of splitting them into six meals seems to yield better metabolic results (Tangvarasittichai, 2015).

Furthermore, a controlled study on men with prediabetes found that a 6 h morning eating window led to more pronounced metabolic improvements than a 12 h schedule, regardless of body weight (Sutton *et al.*, 2018; Parr *et al.*, 2020). Another study comparing equal calorie intake between larger breakfast and smaller dinner consumption revealed superior metabolic marker enhancements, underscoring meal timing and duration's impact on cardiometabolic health. Notably, intermittent fasting showed no safety concerns (Dashti *et al.*, 2019).

Dietary Patterns

Together, in order to maintain the cardiovascular system and overall health, powerful proofs and broad consensus indicate the need to reduce the added sugars and refined cereals consumption and abandon industrial trans fatty acids, replacing them with plant- and animal-based whole foods (Mozaffarian, 2016).

For insulin resistance, a low-carb diet is key in managing glycemia and weight for type 2 diabetes. The recent Consensus Report by the American Diabetes Association and the European Association for the Study of Diabetes supports low-carb diets (<26% of total energy) to treat hyperglycemia and hyperinsulinemia in type 2 diabetes (Kelly *et al.*, 2020).

The "Mediterranean diet," paired with extra virgin olive oil and nuts, commonly lowers cardiovascular diseases and apolipoprotein B levels. Yet, it's worth noting the diet's diversity, Mediterranean origins, and applicability across a diverse global population (Widmer *et al.*, 2015).

Emerging research in both animals and humans suggests that time-limited diets offer cardiometabolic benefits. Ketogenic diets notably mimic fasting-related biochemical traits, influencing pathways linked to longevity and cardiovascular health. Nutritional ketosis suppresses growth-related pathways (insulin, IGF-1, mTOR), activates AMP-Activated Protein Kinase (AMPK), and triggers antioxidant gene expression. BHB appears pivotal in mediating the benefits tied to nutritional ketosis and calorie restriction (Kosinski and Jornayvaz, 2017; Becker *et al.*, 2021).

Nutritional Compounds as Therapeutic Options

We summarized the most important potential beneficial effects of various nutritional compound groups in Table 1. Also, the scheme of the role of various compound groups in atherosclerosis inhibition is represented in (Fig. 1).

Omega-3

Omega-3 and omega-6 are the essential types of polyunsaturated fatty acids (PUFAs). Omega-3 includes α -Linolenic Acid (ALA), eicosapentaenoic acid (EPA), and Docosahexaenoic Acid (DHA), while omega-6 consists of linoleic acid and arachidonic acid (Balić *et al.*, 2020).

Table 1: Nutritional compounds and their effects on cardiovascular health

Nutritional compound	Products	Potential benefits	References
Omega-3	Flaxseed, soybean and canola oils, fish, fish oil, krill oil	Reduction in markers of atherothrombotic risk, reduction in the concentrations of several markers of inflammation	Balić <i>et al.</i> (2020); Sokoła-Wysoczańska <i>et al.</i> (2018); D'Angelo <i>et al.</i> (2020); Innes and Calder (2020); Golanski <i>et al.</i> (2021); Chaudhary <i>et al.</i> (2019); Preston Mason (2019); Paulo <i>et al.</i> (2008); Tousoulis <i>et al.</i> (2014); Violi <i>et al.</i> (2023); Siniarski <i>et al.</i> (2018); Cawood <i>et al.</i> (2010); Chistiakov <i>et al.</i> (2015a; 2014); Thies <i>et al.</i> (2003); Nozue <i>et al.</i> (2013); Zhao <i>et al.</i> (2009); De Luis <i>et al.</i> (2009); Bouwens <i>et al.</i> (2009); Myasoedova <i>et al.</i> (2016); Bradberry and Hilleman (2013)
Omega-6	Safflower, corn oil, poultry, meat, and eggs	Positive effect on the markers of inflammation of highly sensitive C-Reactive Protein (hs-CRP) and oxidative stress	Shramko <i>et al.</i> (2020); Mariamenatu and Abdu (2021); Hooper <i>et al.</i> (2018); Visioli and Poli (2020) Chistiakov <i>et al.</i> (2012; 2015b); Rupp <i>et al.</i> (2004); Sluijs <i>et al.</i> (2010); Eftekhari <i>et al.</i> (2013); Ruiz-León <i>et al.</i> (2019); Varela-López <i>et al.</i> (2016); Hidaka <i>et al.</i> (2008)
Coenzyme Q10	Fruits, vegetables, cereals and dairy products	In individuals with hyperlipidemia and myocardial infarction can experience improvements in the blood pressure and serum lipoprotein levels after a 12-week intervention; Significantly lowered total and LDL cholesterol reduced fibrinogen levels and raised HDL cholesterol	Mohseni <i>et al.</i> (2015); Pérez-Sánchez <i>et al.</i> (2017); Lee <i>et al.</i> (2012); Larijani <i>et al.</i> (2013); Zozina <i>et al.</i> (2018); Ozkanlar and Akcay (2012); Tan and Norhaizan (2019); Puchenkova <i>et al.</i> (2020)
Vitamins	Various products depending on the group of vitamins	Decreased damage to Endothelial Cells (EC); modulation of the immune system response, and preserve the proliferation and migration of Vascular Smooth Muscle Cells (VSMC); enhanced production of Nitric Oxide (NO) and suppressed formation of modified LDL	Cheng <i>et al.</i> (2017)
Carotenoids	Fruits and vegetable	Slowed Down Development of atherosclerosis; significant improvement in LDL cholesterol, a decrease in IL-6 and an increase in FMD	Zou <i>et al.</i> (2011); Rubin <i>et al.</i> (2017)
Phytosterols	Plant food sources	Dose-dependent reduction in total cholesterol and LDL cholesterol	Gylling and Simonen (2015); Sobenin <i>et al.</i> (2014); Lambert <i>et al.</i> (2017); Plana <i>et al.</i> (2008); Heggen <i>et al.</i> (2010); Vilahur <i>et al.</i> (2019)
Stilbenes	Red wine, grapes, peanuts and berries	Anti-inflammatory and antioxidant effects	Koushki <i>et al.</i> (2018); Mohammadi-Sartang <i>et al.</i> (2017); Dyck <i>et al.</i> (2019); Macedo <i>et al.</i> (2017); Sobenin <i>et al.</i> (2013a; 2012); Espinoza <i>et al.</i> (2017); Van der Made <i>et al.</i> (2017); Soldatov <i>et al.</i> (2018a); Kitada <i>et al.</i> (2017); Kjær <i>et al.</i> (2017); Imamura <i>et al.</i> (2017); García-Martínez <i>et al.</i> (2021)
Flavonoids	Tea, fruit, vegetables, grains, legumes nuts and wine	Decrease in cardiovascular mortality; a significant decrease in the risk of mortality from coronary heart disease and a significant decrease in the risk of stroke	Panche <i>et al.</i> (2016); Mutha <i>et al.</i> (2021)

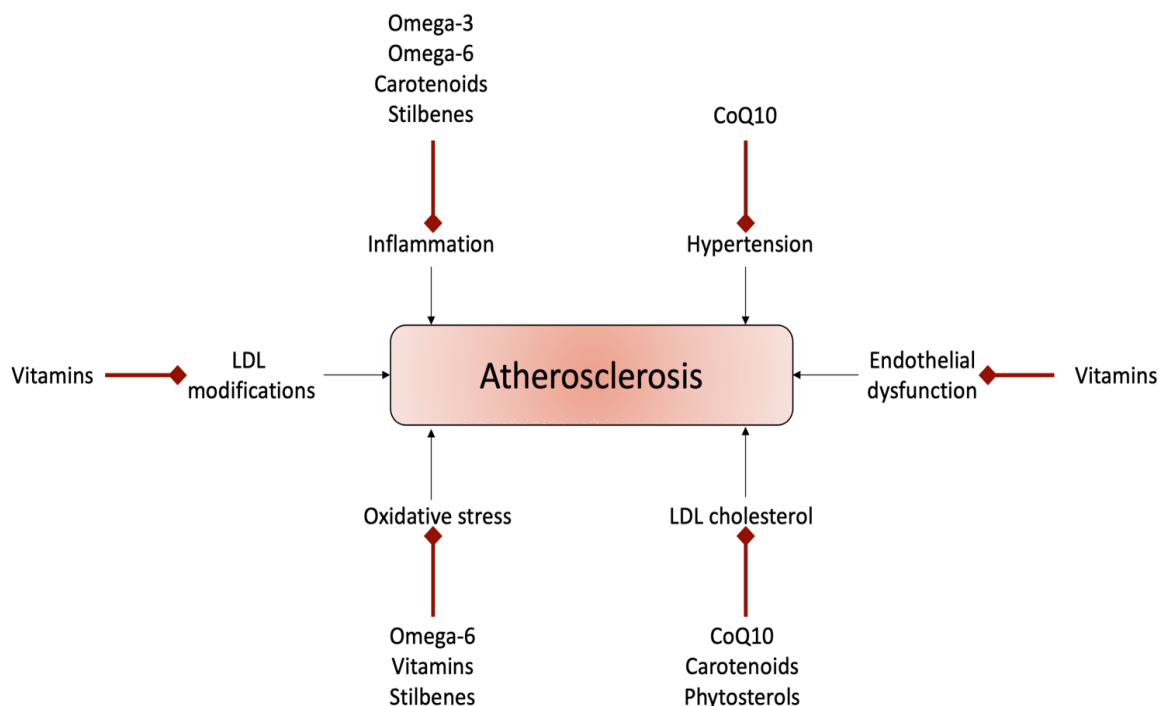


Fig. 1: Implication of various compound groups in atherosclerosis inhibition

Flaxseed, soybean, and canola oils are good sources of essential fatty acids, which can be converted into EPA and DHA in the liver. EPA and DHA can be obtained from fish, fish oil, krill oil, omega-3-enriched foods, or dietary supplements (Sokoła-Wysoczańska *et al.*, 2018).

Most chronic diseases (such as cardiovascular disease and cancer) may correlate with the ratio of ω -6/ ω -3, but the most favorable ratio has yet to be established (D'Angelo *et al.*, 2020).

Marine omega-3 supplements have strong scientific support for preventing cardiovascular diseases. However, conflicting results in large studies may be attributed to variations in study design, participant populations, inadequate doses (<1000 mg), and duration of supplementation (Innes and Calder, 2020).

Omega-3 FA has been linked to multiple mechanisms that contribute to their anti-inflammatory effect in atherosclerosis. These mechanisms encompass improvements in lipid profile, blood pressure, endothelial function, reduction of pro-inflammatory biomarkers, and promotion of plaque stability (Golanski *et al.*, 2021).

Research observations have found that the addition of omega-3 fatty acids is associated with a reduction in markers of atherothrombotic risk. In a study involving 600 men with cardiovascular disease, fish oil supplements were compared in two subgroups: Therapy without lipid reduction and therapy with lipid reduction (Chaudhary *et al.*, 2019). The study showed that participants who did not receive lipid-lowering therapy

had lower levels of various lipid markers and platelet-related factors (Paulo *et al.*, 2008; Preston Mason, 2019).

Multiple mechanisms suggest that omega-3 fatty acids combat atheroma plaque growth. Paulo *et al.* (2008) studied 275 healthy Europeans aged 20-40, randomly assigning them to fish oil, lean fish, fatty fish, or a control group (sunflower oil capsules).

After 8 weeks, the lean fish group showed a 5% decrease in sICAM-1 densities, while the fatty fish and fish oil groups did not show significant changes.

The group consuming fatty fish and fish oil, however, exhibited significant increases of 16.1 and 21.9% in sVCAM-1 concentrations. Additionally, a controlled trial found that the addition of omega-3 fatty acids resulted in a significant reduction in SP-selectin, particularly in men. In women, the introduction of different amounts of omega-3 fatty acids led to significant reductions in sICAM-1 concentrations and increases in sVCAM-1 concentrations. Yusof *et al.* (2008) also noted a slight reduction in sICAM-1 levels in the blood plasma of 10 healthy middle-aged men after administering specific doses of EPA and DHA for 8 weeks.

Omega-3 fatty acids have shown a significant impact on inflammation markers associated with atheroma progression and plaque stability. In a double-blind study by Tousoulis *et al.* (2014), 29 patients with metabolic syndrome were given 2 g/day of omega-3 fatty acids for 12 weeks. The treatment resulted in decreased IL-6 levels and increased PAI-1 levels in plasma. Additionally,

several studies have reported improved endothelial function, measured by an increase in FMD, with omega-3 fatty acid supplementation.

In a study involving 36 very high-risk patients with ASCVD and T2DM, (Violi *et al.*, 2023; Siniarski *et al.*, 2018) found no substantial alterations in parameters related to endothelial function, including FMD and NMD, after a three months administration of 2 g of omega-3 fatty acids (1000 mg DHA + 1000 mg EPA). However, Cawood *et al.* (2010) demonstrated that increased levels of EPA are associated with reduced inflammation, improved plaque stability decreased T-cell infiltration, and fewer foam cells, as supported by studies conducted by Chistiakov *et al.* (2014; 2015a).

Thies *et al.* (2003) ran a randomized controlled trial with individuals prepping for CEA, drawing similar findings. They randomly gave either fish oil (ω -3), oil sunflower (ω -6), or placebo capsules to participants for around 42 days pre-surgery.

The group taking fish oil exhibited enhanced plaque stability, marked by thinner fibrous caps and less inflammation as reduced lymphocyte infiltration and better macrophage suppression compared to control and sunflower oil groups.

In a study by Nozue *et al.* (2013), the ω -6/ ω -3 ratio was directly linked to atherosclerosis development. Zhao *et al.* (2009) studied ω -3's effect on heart failure patients, revealing reduced TNF- α , IL-6, sICAM-1, and NT-proBNP after 3 months. De Luis *et al.* (2009) compared EPA and DHA's impact on at-risk individuals, showing DHA's stronger modulation, lowering CRP, IL-6, TNF- α , and TG while increasing adiponectin and HDL-C. A double-blind study (Bouwens *et al.*, 2009; Myasoedova *et al.*, 2016) with 111 elderly individuals found high EPA + DHA intake altered 1040 genes. Those with 1.8 g EPA + DHA had reduced inflammation and atherogenesis gene expression in PBMCs. Heterogeneity in outcomes stems from factors like dose, source (fish types, oils), additives (EPA, DHA, etc.), population, size, follow-up, and adherence. Omega-3 may aid early atherosclerosis and high-risk populations, but effectiveness could lessen with atherosclerotic disease progression. Additional omega-3 benefits on endothelial function might decrease with existing cardioprotective therapy (Bradberry and Hilleman, 2013).

Omega-6

Increased consumption of omega-6 fats, coupled with a lower intake of saturated fats, has been linked to a reduced frequency of coronary heart disease. However, excessive omega-6 intake may contribute to inflammation and the development of diseases such as cardiovascular disease due to the synthesis of pro-inflammatory eicosanoids. Decreasing the intake of linoleic acid, which reduces Arachidonic Acid (AA) content in tissues, may

potentially lower the risk of coronary heart disease by reducing the production of inflammatory molecules. On the other hand, Dihomo- γ -Linolenic Acid (DGLA), found in omega-6 fatty acids, can be converted into Prostaglandin E1 (PGE1), which has powerful anti-atherogenic properties (Shramko *et al.*, 2020; Mariamenatu and Abdu, 2021).

The effect of omega-6 FA on CVD, particularly atherosclerosis, still lacks a clear conclusion. A systematic review of 19 randomized controlled trials involving 6,461 participants and a follow-up period of 1-8 years did not find any evidence of a dose-dependent or duration-dependent effect on primary outcomes. These outcomes included overall mortality, cardiovascular disease mortality, CAD incidents, strokes, or severe adverse either cardiac or cerebrovascular events. The review indicated that those with initially decreased omega-6 long-chain fatty acid intake could be better protected. Higher omega-6 intake might lower myocardial infarction risk (HR 0.88, 95% CI 0.76-1.02) (Hooper *et al.*, 2018).

While ex-vivo studies have shown a link between diets rich in omega-6 fatty acids and the formation of oxLDL, emerging results suggest that omega-6 fatty acids may have an anti-inflammatory effect, potentially reducing the progression of atherosclerosis (Chistiakov *et al.*, 2012; Visioli and Poli, 2020).

Interventional studies investigating the effects of AA supplementation (840 mg/day for four weeks) did not show any impact on metabolic parameters or platelet function (Rupp *et al.*, 2004). Similarly, studies on Linoleic Acid (LA) supplements have not demonstrated significant effects on reducing atherosclerosis or CVD factors influencing risk.

Sluijs *et al.* (2010) conducted a randomized trial on 401 overweight patients, revealing no impact of cis-9, trans-11 Conjugated Linoleic Acid (CLA) on various factors. In contrast, Eftekhari *et al.* (2013) indicated that adding CLA and omega-3s to diets positively affected inflammation (hs-CRP) and oxidative stress markers in individuals with atherosclerosis.

Due to the heterogeneity of Randomized Controlled Trials (RCTs), varying durations and concentrations of Alpha-Linolenic Acid (ALA) supplements, limited statistical power, and interindividual variability among markers of inflammation, subtle changes may not be easily detected. Genetic factors also play a role in the conversion of Linoleic Acid (LA) to Arachidonic Acid (AA). Some populations have a higher capacity to transform LA to AA, leading to elevated levels of C-Reactive Protein (CRP) and increased cardiovascular disease risk. Further human studies are needed to evaluate the role of omega-6 fatty acids (ω -6 FA) in preventing cardiovascular diseases (Chistiakov *et al.*, 2015b; Ruiz-León *et al.*, 2019).

Coenzyme Q10 (CoQ)

Coenzyme Q, a natural antioxidant, is produced by animals and exists in foods like meat, fish, nuts, and oils.

It's also present in fruits, vegetables, cereals, and dairy. Essential for the mitochondrial electron transport chain, CoQ is tied to cholesterol synthesis through shared intermediates like mevalonate. Among patients who have had experience with statin treatment, a decrease in CoQ10 levels may be observed. Lack of CoQ10 has been associated with cardiovascular diseases, so CoQ10 supplements can be a useful tool for primary prevention of cardiovascular diseases (Varela-López *et al.*, 2016).

Due to challenges in determining the safe Upper Intake Level (UL), studies assess Observed Safe Levels (OSL) to gauge risk. Convincing safety evidence exists up to 1200 mg/day. Yet, CoQ10 levels as high as 3,000 3,000 mg/day have undergone testing without any harmful outcomes and can be regarded as safe (Hidaka *et al.*, 2008).

Numerous intervention studies provide extensive data on CoQ10 supplement potential. To investigate its impact on blood pressure and serum lipoprotein levels in hyperlipidemia and MI, Mohseni *et al.* (2015) conducted a 12-week randomized, double-blind, controlled clinical trial among Iranians.

Patients taking CoQ10 supplements experienced significant reductions in total cholesterol, LDL cholesterol, and fibrinogen, along with increased HDL cholesterol ($p < 0.001$). Both groups displayed raised HDL cholesterol and blood pressure. Pérez-Sánchez *et al.* (2017) highlighted CoQ10's beneficial impact on the function of blood vessel lining and the activity of mitochondria in antiphospholipid syndrome. Lee *et al.* (2012) found that CoQ10 supplementation decreased IL-6 by 14% ($p = 0.03$) in coronary artery disease patients. However, CoQ10 (200 mg/day) didn't significantly improve lipid profile, arterial stiffness, or inflammation markers in obese subjects ($BMI \geq 25 \text{ kg/m}^2$) after 12 weeks.

In the FAITH trial, combining CoQ10 with aged garlic extract reduced CRP and improved endothelial function and pulse wave velocity in intermediate-risk firefighters after 1 year (Larijani *et al.*, 2013).

While meta-analyses and interventions show CoQ10 can substantially reduce CRP, IL-6, and TNF- α and enhance oxidative stress, lipid profile, and blood pressure, consider their heterogeneity, short intervention periods, varied doses, limited RCT subjects, and study number.

These factors might contribute to CoQ10's neutral impact on proinflammatory biomarkers. Thus, the absence of consistent studies demonstrating CoQ10 supplement benefits in atherosclerosis prevention currently restricts its nutraceutical use. However, ample scientific evidence suggests combining statin therapy with CoQ10 supplements could aid in further reducing the atherosclerotic process (Zozina *et al.*, 2018).

Vitamins

Vitamin intake is proven to be useful in the prevention of CVD. Vitamins are able to decrease damage to

Endothelial Cells (EC), modulate the immune system response, preserve the proliferation and migration of Vascular Smooth Muscle Cells (VSMC), enhance the production of Nitric Oxide (NO), and suppress the formation of modified LDL. Indeed, a lack of vitamins A, C, E, and K is linked to a higher risk of cardiovascular disease. Although vitamin A supplementation is effective in animal models against atherosclerosis, human trials lack this evidence. Low dietary antioxidant vitamin intake is also tied to faster atherosclerosis development (Ozkanlar and Akcay, 2012).

Carotenoids

Carotenoids are a vast family of natural pigments that can be divided into carotenes (α -carotene, β -carotene, lycopene) or xanthophylls (lutein, fucoxanthin, canthaxanthin, zeaxanthin, β -cryptoxanthin, capsorubin, and astaxanthin). Despite the fact that there are more than 500 carotenoids, the human body is able to internalize only 20 of them (Tan and Norhaizan, 2019). Fruits and vegetables are the main dietary sources of carotenoids. These compounds have been associated with beneficial health effects primarily due to their antioxidant properties, along with their function in cellular signaling and the immune system.

Moreover, carotenoids are linked with slowing down the atherosclerosis progression (Shramko *et al.*, 2020).

Siniarski *et al.* (2018) found that tomato-rich diets significantly improved LDL cholesterol, lowered IL-6, and increased FMD. Lycopene-carotenoid supplements were associated with a reduction in systolic BP. However, other inflammation markers showed no significant change. Colmán-Martínez *et al.* (2017) study showed that lycopene-rich tomato juice reduced ICAM-1 and VCAM-1 levels significantly, attributed to the presence of trans-lycopene, while carotene supplementation for 8 weeks did not yield similar results.

ICAM-1 and VCAM-1 levels, along with other vascular function markers, didn't change significantly. In a longer study, kidney transplant recipients taking astaxanthin supplements also showed no significant changes in vascular function markers. However, a study by Zou *et al.* (2011) found decreased carotid artery thickness after 12 months of lutein or lutein plus lycopene supplementation. These changes were linked to serum lycopene levels, suggesting a stronger connection to this carotenoid.

Carotenoids may not be very effective against inflammation and atherosclerosis due to their low bioavailability and plasma concentrations. Differences in absorption, metabolism, and other factors, as well as the type and dose of carotenoid, contribute to varying study results. Current data on carotenoid impact on atherosclerosis progression are inconclusive and more clinical trials are needed (Rubin *et al.*, 2017).

Phytosterols

Phytosterols are biologically active compounds obtained from plant-based sources. Vegetable oils, tubers, legumes, and nuts are rich in phytosterols, while vegetables, fruits, and cereals have lower amounts. Nuts contain free phytosterols that are easily absorbed.

In the Western diet, people typically consume approximately 296 mg of phytosterols daily, mainly campesterol, β -sitosterol, and stigmasterol. Research has shown that phytosterols can lower total cholesterol and LDL cholesterol levels in a manner that depends on the dose.

Consuming 2 g of phytosterols per day can substantially alter cholesterol absorption and lower LDL cholesterol levels in the blood plasma by approximately 8-10%. However, the effects of phytosterols on reducing low-grade inflammation are still uncertain, with conflicting results reported in studies (Sobenin *et al.*, 2014; Gylling and Simonen, 2015).

Several interventional studies have examined the effects of phytosterol intake on cholesterol levels, but no subsequent meta-analyses have been conducted.

Lambert *et al.* (2017) studied overweight/obese individuals in a 4-week crossover design, comparing milk with phytosterols (1.6 g of plant sterols/250 mL of milk) and omega-3 fatty acids. They found reduced pro-inflammatory amyloid P (SAP) levels in Lipoprotein-Depleted Plasma (LPDP). Phytosterols in milk were linked to lower MKP-1 gene expression ($p = 0.026$) and a trend towards increased interleukin 10 receptor (IL-10R) expression ($p = 0.06$), suggesting an anti-inflammatory connection.

In a 4-week trial, Plana *et al.* (2008) gave 18 healthy participants a milk supplement with 2.0 g of free phytosterols. This resulted in a significant decrease in hs-CRP levels by 0.32 mg/L ($p < 0.05$) and an increase in Lipoxin A4 (LXA4) concentration by 0.12 nmol/L ($p < 0.05$), as well as higher nitrites and nitrates ($p < 0.05$, both). However, there were no specific changes in plasma TNF- α levels or markers of oxidative damage. In another study, hypercholesterolemic patients who consumed 3.0 g of phytosterol-enriched margarine daily for 18 weeks did not experience significant changes in inflammation biomarkers (CRP, SAA, IL-6, IL-8, TNF- α and soluble intercellular adhesion molecule-1) compared to a placebo. Low-grade inflammation (-0.04; 95% CI -0.16-0.07) and endothelial dysfunction (-0.2, 95% CI -0.15-0.11) z-scores did not reach statistical significance.

In a study conducted by Heggen *et al.* (2010), two margarines enriched with phytosterols were investigated to assess their impact on endothelial markers and inflammation. The margarine containing rapeseed sterol showed a significant decrease of 8.5% ($p = 0.012$) in serum levels of E-selectin compared to the control group. However, no significant changes were observed in other analyzed markers of inflammation, including VCAM-1,

TNF- α , total PAI-1, and activated PAI-1, following the intervention. Currently, data on the impact of plant sterols, alone or combined with statins, on reducing cardiovascular risk are limited. While in vitro and animal studies suggest anti-inflammatory effects, existing Randomized Controlled Trials (RCTs) on phytosterols/stanols' anti-inflammatory and anti-atherogenic effects are insufficient and conflicting.

Notably, incorporating phytosterols into high-fat spreads shows greater cholesterol reduction compared to free phytosterol uptake (Vilahur *et al.*, 2019).

To ensure unbiased results, various factors like sterol type (phytosterols or phytosterols), study size, participant characteristics, duration, and optimal dosage need consideration. While phytosterol supplements lower lipid levels, especially total and LDL cholesterol, their impact on inflammatory markers lacks reliable evidence. More research is required to explore post-treatment effects in this area.

Stilbenes

Stilbenes are a group of polyphenols having a 1, 2-diphenyl ethylene core. Found in red wine, grapes, peanuts, and berries, these compounds, particularly resveratrol, offer anti-inflammatory and antioxidant benefits that can positively impact health, including atherosclerosis. In vitro studies conducted on animals have yielded promising results, however, these results undoubtedly have to be confirmed by clinical trials (Koushki *et al.*, 2018). Adipokine levels, particularly the leptin-to-adiponectin ratio, are linked to atherosclerosis and cardiovascular risk. Resveratrol has been linked to alterations in these cytokines. In a meta-analysis comprising 9 Randomized Controlled Trials (RCTs) conducted by Mohammadi-Sartang *et al.* (2017), it was observed that a higher intake of resveratrol supplements (≥ 100 mg/day) led to a notable increase in adiponectin levels [1.11 mcg/mL (95% CI 0.88, 1.34)]. Nevertheless, when taking resveratrol, regardless of the dose, the levels of leptin in the blood plasma did not change significantly.

Numerous RCTs on the effects of stilbene supplements, in particular resveratrol, have been conducted over the past few years. Supplementation doses ranged from 40-1500 mg/day, with intervention periods spanning several hours to 3 months. In addition, the results obtained from different studies gave different results (Dyck *et al.*, 2019).

Macedo *et al.* (2017) conducted a study among healthy adults in which the effect of taking 100 mg of trans-resveratrol daily for 3 months was observed. However, they did not establish important changes in the metabolic parameters and markers of inflammation and oxidation analyzed in comparison with the controls. One exception is the activity of GPx, which serves as a marker of oxidative stress and exhibited a significant decrease

compared to the placebo group ($p < 0.05$). However, the precise cause of this change remained unclear. A fitness test revealed reduced GPx activity and TNF- α concentration, along with elevated blood plasma glucose levels. The authors of the study proposed that the fitness test employed might not have been sufficiently comprehensive to evaluate the potential influence of resveratrol on the antioxidant systems of the participants (Sobenin *et al.*, 2012; 2013a-b).

In a small study by Espinoza *et al.* (2017) involving only nine participants, a higher dosage of resveratrol (1 g/day) administered over four weeks led to a modest but significant decrease in TNF- α and MCP-1 levels ($p < 0.05$). However, these changes were not sustained over time. In contrast to (Macedo *et al.*, 2017) this study observed an increase in overall antioxidant capacity. Van der Made *et al.* (2017) explored the effects of 150 mg of trans-resveratrol over four weeks on overweight and obese patients (BMI 28.3 ± 3.2 kg/m²) as well as healthy adults. The results showed no significant alterations in markers of inflammation or endothelial function, although there was an increase in diastolic blood pressure and heart rate ($p < 0.05$). Subgroup analyses based on sex or BMI (\geq or $<$ 30 kg/m²) did not yield significant differences (Soldatov *et al.*, 2018a-b). Kitada *et al.* (2017) employed piceatannol, a resveratrol analog, and reported improved insulin sensitivity in overweight men, with a reduction in plasma insulin levels by $-18.8 \pm 11.2\%$ ($p = 0.02$) and HOMA-IR by $-17.2 \pm 11.5\%$ ($p = 0.02$). However, studies involving patients with type 2 diabetes did not show significant changes. Bo *et al.* (2016) evaluated the effects of resveratrol (500 and 40 mg/day) in patients with type 2 diabetes over six months. While there were no significant differences in metabolic and inflammatory markers, pentraxin 3 levels and overall antioxidant status increased ($p < 0.05$). Notably, high-dose resveratrol supplementation resulted in a significant increase in total cholesterol levels (11.94 mg/dL; 95% CI 2.55; 21.33), consistent with findings from Kjær *et al.* (2017), who observed elevated total cholesterol, LDL cholesterol, and fructosamine levels in patients with metabolic syndrome receiving 1g/day of resveratrol for 16 weeks. Resveratrol intake at doses of 300-500 mg/day led to a reduction in TNF- α levels compared to a placebo, although no similar effect was observed with a dose of 1.5 g/day. The variations in outcomes across studies, influenced by factors such as sample size, participant characteristics, inflammation status, dosage, and treatment duration, may impact the influence of resveratrol on inflammation markers. The limited number of participants in some studies may weaken the statistical power, hindering a comprehensive assessment. Additionally, insufficient resveratrol levels in the bloodstream could account for its limited impact on atherosclerosis markers and

differences in the sources of resveratrol (trans-resveratrol or extracts) with varying compositions might introduce bias (García-Martínez *et al.*, 2021).

Flavonoids

Flavonoids are a vast family of compounds distinguished by a diphenylpropane skeleton (C6-C3-C6). Plant foods are rich in these compounds; a large number of studies have demonstrated that flavonoids have a positive effect on health and contribute to reducing the risk of mortality. However, several meta-analyses, including those by Panche *et al.* (2016); Mutha *et al.* (2021), didn't establish a clear linear dose-response relationship. Regarding cardiovascular diseases, (Grosso *et al.*, 2017; Kim and Je, 2017; Liu *et al.*, 2022; Wang *et al.*, 2014) conducted a meta-analysis of four prospective cohort studies, revealing a link between high flavonoid consumption and reduced cardiovascular mortality. Other prospective studies also showcased lowered coronary heart disease mortality and stroke risk. These findings strongly support a plant-based diet. Future research should delve into specific flavonoid subgroups and assess recent studies on flavonoid supplements and their health effects.

Limitations and Future Perspectives

In this review, we have outlined the potential benefits of nutritional compounds such as vitamins, Co Q10, stilbenes, phytosterols, carotenoids, omega 3, omega 6, and flavonoids. Despite the seemingly obvious benefits of using all these substances, the selection of an adequate diet is a very difficult problem. We have cited several widely used dietary strategies as examples, such as caloric restrictions and specific dietary patterns, such as the Mediterranean diet. Each of these schemes has its positive and negative sides, but finding the perfect balance is extremely difficult. Diets that are predominantly fruits, vegetables, legumes, nuts, seeds, plant-based protein, and oily fish reduce the risk of heart disease, according to the average. Eating more of these foods while reducing your intake of foods high in saturated fat, dietary cholesterol, salt, refined grains and consumption of ultra-processed foods are common components of a healthy diet.

Moreover, a separate problem is precisely the competent design of studies that would need to be carried out for a full and comprehensive assessment of the impact of certain eating patterns. The development of nutritional science faces both intrinsic and pragmatic limitations in conducting rigorous, double-blind, placebo-controlled trials. It is critical to develop and validate new analytical tools and study designs to address the complexities of linking habitual food/nutrient intake with long-term CVD outcomes.

Long-term studies are hampered, firstly, by the lack of a developed study design that would allow assessing all the necessary parameters and secondly, by problems in working directly with patients. Meal modification is a lifestyle change that most patients find difficult to adhere to over a long period of time. In addition, it is also very difficult to control the feeding patterns of free-living populations.

Evaluating these limitations, we would single out long-term studies of the complex impact of dietary patterns on health, including cardiovascular health, as well as the search for biomarkers that would make it possible to make the assessment of the impact of diet more objective as a separate direction for future studies.

Conclusion

Atherosclerosis, type 2 diabetes, and metabolic syndrome are the result of certain metabolic disorders. Of course, an unbalanced diet affects the risk of developing these diseases. Indeed, an unbalanced diet (a diet high in fat and/or carbohydrates) occupies an honorable place among the risk factors for the development of cardiovascular disease.

Many nutrients have been considered in the context of their effectiveness in the fight against atherosclerosis, but a clear answer on their healing effects has not yet been received. After analyzing numerous data on the benefits of certain dietary changes in the prevention of atherosclerosis, as well as its treatment, we clearly believe that maintaining a healthy lifestyle has a positive effect on the risk of developing CAD. However, when it comes to treatment, nutrients alone are not enough, and more targeted therapy is needed.

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Author's Contributions

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Ethics

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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