Review

Alpha-linolenic acid and cardiovascular events: a narrative review

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Review

Alpha-Linolenic Acid and Cardiovascular Events: A Narrative Review

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Abstract: Cardiovascular diseases (CVDs) represent the leading cause of global mortality with 1,7 million deaths a year. One of the alternative systems to drug therapy to minimize the risk of CVDs is represented by alpha-linolenic acid (ALA), an essential fatty acid of the Omega-3 series, known for its cholesterol-lowering effect. The main purpose of this review is to analyze the effects of ALA and investigate the relevant n-6/n-3 ratio in order to maintain functionally beneficial effects. Concerning the lipid-lowering preventive effects, ALA may favorably affect the values of LDL-C and triglycerides in either adult and pediatric populations and it has a positive and protective effect against hypertension, suggesting that ALA is an useful diet-related antihypertensive compound. According to the 2009 EFSA statement, dietary ALA may contribute to reducing the risk of CVDs, thanks to anti-hypertensive, anti-atherosclerotic and cardio-protective effects.

Keywords: alpha-linolenic acid; hempseed oil; cardiovascular events; LDL-cholesterol; TC-cholesterol; cardioprotective effect; heart disorders; linoleic acid

1. Introduction

Cardiovascular diseases (CVDs) represent the primary cause of global mortality, as they are responsible for about 1,7 million deaths a year, and the major contributor to reduced quality of life [1,2].

CVDs include ischemic heart disease (IHD), stroke, heart failure, peripheral arterial disease, and several other cardiac and vascular conditions. As of 2023, the American Heart Association identifies CVDs as the leading cause of death in the United States, accounting for 928.741 deaths in 2020. Between 2018 and 2019, direct and indirect costs of total CVD were $407.3 billion ($251.4 billion in direct costs and $155.9 billion in lost productivity/mortality) [3].

In addition to conventional pharmacological therapy (ACE inhibitors, beta-blockers, statins, fibrates and PCSK9 inhibitors), nutraceutical solutions have been proposed in recent years as contributing factors to reduce cardiovascular risk [4,5]. Accordingly, nutraceuticals may act on the reduction of lipid risk markers, including Total Cholesterol (TC), Low-Density Lipoprotein (LDL-C), and triglycerides (TG) and can be divided on the basis of their mechanism of action.

For instance, sterols and glucomannan may reduce LDL-C by decreasing the intestinal absorption of endogenous cholesterol, competing in the formation of solubilized micelles [6,7], which interact with the membrane and are the substrate of the Niemann-Pick C1-Like 1 (NPC1L1) transporter that facilitates the transport of sterols from the intestinal lumen. Red yeast rice, garlic, panthetine, and policosanols (mimicking statin action) inhibit hepatic cholesterol synthesis. These types of nutraceuticals have a reversible inhibitory action on 3-Hydroxy-3-Methyl-Glutaryl-CoA (HMG-CoA) reductase, the key enzyme in the synthesis of endogenous cholesterol. Food

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supplements usually derived from red yeast rice contain a concentration of monacolins up to 1,9% [8].

Berberine may induce LDL-C excretion, with the same mechanism as soy [9,10,11].

Berberine acts directly on the expression of the LDL receptor (LDL-R) an up-regulation of the receptors through a post-transcriptional mechanism that stabilizes their mRNA.

Recent studies have underlined that it reduces the intestinal absorption of cholesterol, increasing fecal excretion and promoting its hepatic turnover and the formation of bile acids [9].

Similarly, plant-derived polyunsaturated fatty acids (PUFAs) may share analogous functional effects. The human body possesses the capacity to endogenously synthesize the amount of required fatty acids, except for linoleic acid (LA), the precursor of the Omega-6 fatty acids, and alpha-linolenic acid (ALA), the precursor of the Omega-3 fatty acids. Since these compounds must be introduced with diet, they are called essential fatty acids (EFAs).

LA and ALA are in competition, as they are metabolized by the enzyme delta-6-desaturase. This has been suggested to be important for health, as a high intake of LA may reduce the amount of the enzyme available for ALA metabolism, so increasing the risk of heart disease through mechanisms mainly associated with pro-inflammatory conditions [12,13,14]. Evidence supporting this theory shows that over the past 150 years, Omega-6 intakes through today's diet have increased, while Omega-3 intakes have decreased in parallel with the increase in heart disease. Thus, the concept of an "ideal" ratio of n-6/n-3 in the diet was developed and is between 10:1 and 5:1[15,16]. Within this context, while the functional effects of LA are well-known [17,18,19,20,21], ALA, present in hempseed oil (HSO), walnuts, olive and flaxseed oils, has less known, but still relevant, functional effects. Nuts and seeds are important sources of ALA and other micronutrients, such as sterols, fibers and polyphenolic compounds. These nutrients are effective in protecting against cardiovascular, inflammatory, and chronic diseases [22,23,24]. Regarding the ALA content of nuts and seeds, 28 g of hempseed, or walnuts exceeds the Adequate Intake for ALA, which is 1.1 g/day for women, and 1.6 g/day for men [25,26]. Oils rich in ALA, such as flaxseed and hempseed ones, are effective in analyzing the effects of ALA. Flaxseed, hempseed and canola oil are the main sources of ALA; soybean oil is often considered to be a low to moderate source of this nutrient, as studies of its fatty acid composition have shown ALA concentrations ranging from 2.7% to 7.8% [27,28]. These dietary sources of ALA may also be relevant during pregnancy and breastfeeding women, not only because of their rich nutritional composition, but also because of the well-founded need to avoid complex mixtures of herbal supplements that may jeopardize the health of both mother and child. In addition, plant sources of omega-3 PUFAs could be considered an effective option for women who cannot tolerate fatty fish and for those who suffer from nausea, common manifestation during pregnancy [29,30]. Exclusively vegan diets should be evaluated carefully because of the risk of n-3 PUFA deficiency. In addition to lower intakes of total and saturated fats, another characteristic of exclusively vegan diets is a higher proportional intake of n-6 PUFAs compared to vegetarian diets [31,32]. For these reasons, recommendations for vegan diets that include adequate amounts of ALA are of paramount importance for the maintenance of long-term health [33].

Therefore, the main purpose of this narrative review is to analyze the effects of ALA and investigate the relevant n-6/n-3 ratio in order to maintain functionally favorable effects [34,35,36].

Functional Effects of ALA

We selected different studies about ALA and its effects on the cardiovascular system and categorized them by effects, on risk factors for CVD, and direct cardioprotection, respectively.

Risk Factors for Cardiovascular Disease

The most important claim declared by EFSA concerning ALA is related to the influence on blood cholesterol concentrations (EFSA 2009; 7(9):1252) [37]. Specifically, the claim indicates that ALA contributes to the maintenance of normal blood cholesterol levels. (*Figure 1*)

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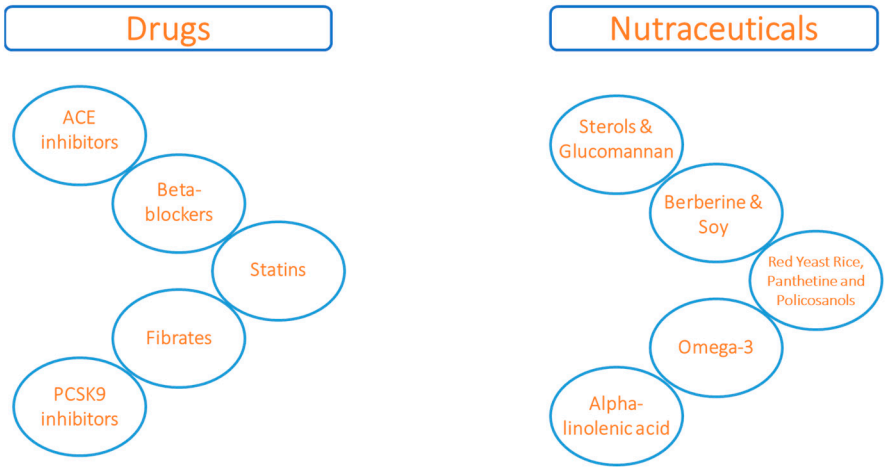

Figure 1. Drugs and nutraceuticals for treating heart failure and lipid risk markers.

(A cause-effect relationship between the dietary intake of ALA and the reduction of plasma concentrations of TC and LDL-C has been recognized. Studies issued after the EFSA statement further suggest that ALA has anti-proliferative [38], anti-hypertensive [39,40,41], anti-atherosclerotic [42], cardioprotective effects [42,43,44,45,46], and it successfully improves the composition of the red cell membrane in children with hyperlipidemia [47], possibly reducing the risk of cardiovascular events in adulthood. In a pilot study by Del Bo' et al [47], a randomized clinical trial (RCT), 8 week-long, dietary intervention study aimed to evaluate the impact of HSO supplementation on the lipid profile and fatty acid composition of red blood cells (RBCs) in children and adolescents with primary hyperlipidemia. The 36 study subjects aged 6 to 16 years were divided into 2 different groups: the control group and the HSO one, receiving 3 g of HSO with 1.4 g of linoleic acid (LA) and 0.7 g/day of ALA. Both groups received specific dietary guidelines. Blood samples were kept for each subject, before and after administration with HSO, in order to analyze the lipid profile, composition of RBCs, and omega-3 index After an eight-week supplementation with HSO, there were significant reductions in the RBC content of total saturated and monounsaturated FAs (−5.02 ± 7.94% and − 2.12 ± 2.23%, respectively). Conversely, the levels of total n-3 and n-6 PUFAs increased (+1.57 ± 1.96% and + 5.39 ± 7.18%, respectively), as did the Omega-3 index (+1.18 ± 1.42%). This study confirms that diet represents the first line of therapy for primary hyperlipidemia.

In the clinical study by Yue et al of 2021 [48], the effect of ALA intake on blood lipid profiles was examined, especially on triglycerides (TG), TC, HDL-C, LDL-C, VLDL-C, and the ratio of TC to HDL-C. 1305 subjects were enrolled in the ALA group and 1325 in the control one were identified. Compared with the control group, dietary intake of ALA significantly reduced the concentrations of TG (WMD −0.101 mmol/L; 95% CI: −0.158 to −0.044 mmol/L; P = 0.001), TC (WMD −0.140 mmol/L; 95% CI: −0.224 to −0.056 mmol/L; P = 0.001), LDL-C (WMD −0.131 mmol/L; 95% CI: −0.191 to −0.071 mmol/L; P < 0.001), VLDL-C (WMD −0.121 mmol/L; 95% CI: −0.170 to −0.073 mmol/L; P < 0.001), TC/HDL-C ratio WMD −0.165 mmol/L; 95% CI: −0.317 to −0.013 mmol/L; P = 0.033) and LDL-C/HDL-C ratio (WMD −0.158 mmol/L; 95% CI: −0.291 to −0.025 mmol/L; P = 0.02). ALA has no effect on HDL-C (WMD 0.008 mmol/L; 95% CI: −0.018 to 0.034 mmol/L; P = 0.541). Dose-response analysis showed that 1 g/day increase in ALA was associated with reductions in TG of 0.0016 mmol/L 0.0071 mmol/L, 0.0015 and 0.0061 mmol/L reduction in TG (95% CI: −0.0029 to −0.0002 mmol/L), TC (95% CI: −0.0085 to −0.0058 mmol/L), HDL-C (95% CI: −0.0020 to −0.0011 mmol/L) and LDL-C (95% CI: −0.0073 to −0.0049 mmol/L) levels, respectively. The effects of ALA intake on TG, TC, and LDL-C concentrations were pronounced in patients with hyperlipidemia or hyperglycemia compared to healthy subjects. Dietary ALA intervention improved blood lipid profiles by reducing levels of TG, TC, LDL-C and VLDL-C. These results show that increasing ALA intake could potentially prevent the risk of CVDs.

In a meta-analysis of controlled trials conducted by Khalesi et al [49] the intake of ALA-rich sesame fractions is associated with a reduction of TG. As a result, the consumption of sesame did not

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significantly change the TC (-0.32 mmol/L, 95% CI: -0.75 to 0.11; p=0.14, I2 =96 %), LDL-C (-0.15 mmol/L, 95 % CI: -0.50 to 0.19; p = 0.39, I2 = 96 %) or HDL-C levels (0.01 mmol/L, 95% CI:-0.00 to 0.02; p= 0.16, I2 = 0 %). However, a significant reduction was observed in serum TG levels (-0.24 mmol/L, 95 % CI: -0.32 to -0.15; p <0.001, I2 = 84 %) after consumption of sesame. Although the consumption of sesame rich in ALA seems to significantly reduce blood TG levels, there is not enough evidence to support its hypocholesterolemic effects.

Importantly, the positive effects of ALA can also be extended to non-lipid outcomes as well. Experiments show that ALA stimulates nitric oxide (NO) production [50,51], and increases action mediated by prostanoids, with effects on platelet aggregation and coagulation. Therefore, it reduces the probability of thrombotic events, regulates the heart rhythm and decreases the onset of arrhythmias and inflammation, with a direct action on prostaglandins [39,52]. Recent evidence agrees that the intake of PUFAs has cardioprotective effect, through mild lowering blood pressure (BP). Cicero et al [39] evaluated the long-term effect of a PUFA intake on the BP of 111 subjects with hypertriglyceridemia. Subjects were treated with 2 g PUFA/day to improve lipid profile. Following 12 months of treatment, the systolic blood pressure (SBP) exhibited a mean reduction of 2.7 ± 2.5 mmHg (p = 0.001), and the diastolic blood pressure (DBP) decreased by 1.3 ± 3.3 mmHg (p < 0.001). Additionally, the basal heart rate decreased by 4.0 ± 4.4 bpm (p < 0.001). Both the reductions in SBP and DBP were significantly correlated with the baseline SBP (p < 0.001) and DBP (p < 0.001), respectively. In this retrospective study, PUFA supplementation for 1 year led to a significant reduction in SBP, DBP, pulse pressure (PP), and basal heart rate in hypertriglyceridemic patients with normal-high blood pressure.

Additionally, a series of studies aimed to understand how the intake of ALA in the diet was useful in tracing BP and in increasing the aortic thickness of the intima and media tunica in Small Gestational Age (SGA) infants [39,40]. In this study of 2015 by Skilton et al [40], 1009 participants were recruited at 6 months and were followed until age 19 years. The purpose of this study is to evaluate a possible association between dietary ALA intake, low BP and aortic intima-media thickness in children born with SGA. Blood pressure and food records were assessed at each visit. A total of 1009 participants had at least one blood pressure measure and complete birth weight and gestational age data, including 115 (11%) SGA. These children had greater systolic and PP from age 14 years onwards. In those born with SGA, SBP was 2.1 mmHg lower ([95% CI 0.8-3.3]; P=.001) and PP 1.4 mmHg lower ([95% CI 0.3-2.4]; P=.01), per exponential increase in ALA intake. It can be concluded from the study that ALA supplementation during childhood improves cardiovascular health of children with SGA.

Flaxseed and HSO contain Omega-3 fatty acids, lignans, and fiber, which together may be beneficial for patients with CVDs. Hypertension is often associated with peripheral artery disease. Rodriguez-Leyva and colleagues [41], aimed to investigate the effects of daily flaxseed intake on SBP and DBP in patients with peripheral artery disease. In this prospective, double-blinded, placebo-controlled, randomized trial, 110 patients consumed a variety of food containing 30 g of ALA or placebo daily for 6 months. Plasma levels of Omega-3 ALA increased 2- to 50-fold in the flaxseed-fed group but did not increase significantly in the placebo group. SBP was ≈ 10 mmHg lower, and DBP was ≈ 7 mmHg lower in the flaxseed group compared with placebo at 6 months. Enrolled patients with an SBP ≥ 140 mmHg at baseline achieved a significant reduction of 15 mmHg in SBP and 7 mmHg in DBP with flaxseed supplementation. These results confirmed that ALA is one of the most powerful antihypertensive agents achieved by a dietary intervention.

A very important study that examined changes in atherosclerosis markers was the MARGARIN trial [53], conducted on 110 subjects with a high risk of IHD. The experimental group received margarine (80% fat, of which 60% as PUFAs) containing either 15% or 0.3% of total fat as ALA for two years. Results showed that the intake of ALA reduced C-reactive protein, a marker of inflammation, but the present study found no effect on markers of atherosclerosis.

Cardioprotective Effect

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The 2020-2025 American Dietary Guidelines showed that there is strong evidence to demonstrate that replacing Saturated Fatty Acids (SFAs) with PUFAs reduces the risk of IHD events and CVD mortality [54]. In high-risk patients, ALA prevents coronary heart disease (CHD), considered one of the major causes of death worldwide [41,42,43,45,55,56].

The aim of the study by Vedtofte et al [55] was to examine the association between ALA intake and the risk of CHD. Data from eight American and European prospective cohort studies including 148.675 women and 80.368 men were used. During 4-10 years of follow-up, 4.493 CHD events and 1.751 CHD deaths occurred. Among men, the researchers found an inverse association between ALA intake and CHD events and deaths. Each additional gram of ALA was associated with a 15% lower risk of CHD events (HR: 0.85; 95% CI: 0.72, 1.01) and a 23% lower risk of CHD deaths (HR: 0.77; 95% CI: 0.58, 1.01). The Cardiovascular Health Study [31] was designed to examine the associations of dietary ALA with the risk of mortality, CHD and stroke among older adults who participated in the study, a cohort study of 2709 adults aged ≥ 65 years. After adjustment for age, sex, race, enrollment site, education, smoking status, diabetes, Body Mass Index (BMI), alcohol consumption, treated hypertension and total energy intake, higher dietary ALA intake was found to be associated with a lower risk of total and non-cardiovascular mortality. When the highest quintile of dietary ALA was compared with the lowest quintile, the HR for total and non-cardiovascular mortality was found to be 0.73 (95% CI: 0.61, 0.88) and 0.64 (95% CI: 0.52, 0.80), respectively. In conclusion, this study suggests that dietary ALA is associated with a lower risk of total and non-cardiovascular mortality in older adults.

In a 2012 meta-analysis of observational studies by Pan et al [42], increasing dietary ALA was associated with a moderately lower risk of total CVD (RR: 0.90; 95% CI: 0.81, 0.99). 27 studies were analyzed, including 251.049 individuals and 15.327 CVD events. The association between ALA intake and reduced risk of CVD was significant in 13 comparisons, but 17 comparisons show similar but non-significant trends Therefore, considering observational studies, higher ALA intake is associated with a moderately lower risk of CVD.

In the study by Zelniker et al of 2021 [57], patients with acute coronary syndrome, after intake of n-3 PUFAs, were associated with a lower risk of cardiovascular death (OR: 0.82; 95% CI: 0.68, 0.98 per 1-SD increment), whereas an attenuated relation was observed after administration of ALA (OR: 0.92; 95% CI: 0.74, 1.14).

In the European Prospective Investigation into Cancer and Nutrition (EPIC) study [58] which included 22.043 subjects in Greece, there were 275 deaths after 44 months. These individuals consumed a traditional Mediterranean diet rich in ALA, there was a significant reduction in total mortality, death from CHD of 25% and 33%, respectively. In 1302 individuals with known CHD, there was a reduction in total mortality and CHD of 27% and 31%, respectively [59].

The Lyon Diet Heart Study [60] was an effective study in demonstrating the efficacy of a Mediterranean-style diet supplemented with ALA on composite measures of IHD recurrence after a first MI. Subjects in the experimental group were instructed to follow a Mediterranean diet and were given a canola oil-based margarine containing 4.8% ALA. After 46 months of this diet, these subjects have 50-70% lower risk of recurrent IHD [61]. Only ALA was significantly associated with improved prognosis (RR for the composite of cardiac death and nonfatal acute MI: 0.20; 95% CI: 0.05, 0.84) when plasma fatty acids were analyzed as crude estimates of dietary data.

Another systematic review and meta-analysis of cohort studies by Jingkai et al [56] examined an overall association between ALA intake and CHD risk, assessing dose-response relationships. 14 studies of 13 cohorts were identified and included in the meta-analysis. The pooled results showed that higher ALA intake was associated with a modestly reduced risk of combined CHD (risk ratios (RR)=0.91; 95 % CI: 0.85, 0.97) and fatal CHD (RR=0.85; 95 % CI: 0.75, 0.96). Compared with individuals with lower ALA intake, only subjects with ALA intake < 1.4 g/d showed a reduced risk of composite CHD. ALA intake was linearly associated with fatal CHD, and each 1 g/d increase in ALA intake was associated with a 12% reduction in the risk of fatal CHD (95 % CI: -0.21, -0.04).

To better understand the role of ALA, Sala-Vila et al [62] prospectively evaluated the association between dietary ALA and fatal CVD in participants of the PREvèncion with DIeta MEDiterranea

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(PREDIMED) study (n=7202). These results showed that dietary ALA at > 0.7% of daily energy intake was associated with a 28% reduced risk of all-cause mortality. Participants (n=7447) at high CVD risk in a treatment arm receiving 30 g/day of mixed nuts (15 g walnuts, 7.5 g hazelnuts, and 7.5 g almonds) had a reduced incidence of cardiovascular events (HR: 0.72; 95% IC: 0.54, 0.95) with 4.8 daily grams of ALA consumption compared to the control group. In the intervention group, dietary ALA increased by 0.43 g/day and plasma ALA increased by 0.30% - 0.44% in a random subsample [63]. In addition,, several studies have examined the association between ALA intake and CHD risk and evaluated a possible dose-response relationship. Results showed that higher intakes of ALA were associated with a modestly reduced risk of composite coronary disease (RR=0.91; CI 95 % 0.85, 0.97) and fatal coronary disease (RR=0.85; 95 %; CI 0.75, 0.96). Subjects who consumed ALA < 1.4 g/day had a significant risk reduction, in contrast to those who did not include ALA in their diet [64].

Regarding ALA and its association with cardiovascular risk, there is the hypothesis that ALA may influence cardiovascular risk through effects on arrhythmogenesis and lethal ventricular arrhythmia. Intravenous infusions of ALA reduced the risk of ventricular fibrillation during coronary artery ischemia in different animals, and dietary ALA is associated with a reduced risk of abnormal repolarization in men and women [65]. In addition, after intake, ALA can be converted to EPA and DHA, both of which have antiarrhythmic effects. Other plausible pathways by which ALA may exert beneficial effects on coronary and CVD risk include endothelial function, inflammation, and thrombosis. With respect to CVD, only one large trial has evaluated ALA supplementation for cardiovascular outcomes, including arrhythmias. In the AlphaOmega trial [66], ALA was associated with a significant reduction in arrhythmia-related events compared with placebo or Eicosapentaenoic acid (EPA) and Docosahexaenoic acid (DHA) in post hoc analyses in the subgroup of patients with diabetes, who are particularly prone to ventricular arrhythmias and sudden death after myocardial infarction (MI), (HR: 0.39; 95% CI: 0.17, 0.88). In addition, the results of the study by Kromhout et al [67] suggest and antiarrhythmic effect of ALA intake, but further clinical trials are needed to confirm this. Meta-analyses of observational studies have shown that increasing dietary ALA is associated with a 10% lower risk of total CVD and a 20% lower risk of fatal CHD.

2. Discussion

This narrative review describes the functional effects of ALA in preventing risk factors for cardiovascular diseases, and its direct cardioprotective effects.

Regarding the lipid-lowering preventive effects, this review shows that ALA may favorably affect the levels of LDL-C and TGs in both adult and pediatric populations [47,48, 49]. Dietary ALA intake has a significant effect on the plasma values of LDL-C, TC, and TG levels, as well as on the improvement of erythrocyte membrane composition. However, the reduction of cholesterol and triglyceride levels may also depend on the plant source of ALA used. For example, HSO allows for a significant reduction of LDL-C, TC, and RBC, while sesame seeds are effective in reducing triglyceride levels, but not other cholesterol-rich fractions.

A beneficial and protective effect against hypertension has been reported in three studies [39,40,41]. All of them confirm that daily consumption of ALA reduces SBP and DBP, possibly through the release of NO, a potent vasodilator. The results were also confirmed in subjects with borderline BP values, suggesting that ALA is an effective dietary antihypertensive compound.

With regard to cardioprotective effects, the studies and meta-analyses [41,42,43,45,55,56,57,58,59,60,61,62,63,64] reported by us, show controversial results. While some studies confirm an important association between daily ALA intake and a significant reduction in CVD risk, others indicate that there is no strong correlation. A dose-dependent dietary intake of ALA appears to be associated with a reduced risk of CVD. Some studies confirm that adherence to the Mediterranean diet, with the addition of ALA following the correct intakes, has positive and beneficial effects on significantly reducing IHD, cardiac death and nonfatal acute MI. Although some studies are significant and vouch for the effectiveness of ALA, further clinical trials are needed to confirm an between ALA intake, at different doses and CVD events. Eating more ALA, for example, by eating more hempseed or flaxseed oil, probably makes little or no difference in all-cause or

cardiovascular death or coronary events, but slightly reduces CVD, coronary mortality, and heart arrhythmias. The effects of ALA on stroke are unclear, because the evidence was low quality

Three studies [65,66,67] investigated the association between ALA intake and its antiarrhythmic effect, caused, probably, by its direct action on anti-inflammatory eicosanoids. In fact, due to the action of these metabolites, the regulation of heart rhythm is also affected. The anti-inflammatory properties of essential fatty acids, including ALA, are well known. Some of these trials verified that ALA intake was associated with a significant reduction in arrythmia and subsequently MI, while others need further clinical evidence to confirm the efficacy.

ALA has the potential to provide novel and promising research perspectives, which are indirectly related to CVD prevention. A growing body of evidence [68,69,70,71,72,73,74] suggests that ALA intake may be a co-adjuvant intervention to modulate the progression of inflammatory and cancer-related conditions. The effects of n-3 PUFAs on CLSC (cancer stem-like cell) may be an important target for cancer therapy and will be an interesting challenge for future studies, In any case, the antitumor activity of omega-3 PUFAs shown through multiple mechanisms, suggests that they may have an important therapeutic role in the management of CSC (cancer stem cell). At this stage, further large observational and prospective studies are needed to confirm these effective and innovative properties of ALA and to develop RCTs.

3. Conclusions

Based on the studies and research presented herein, increasing ALA in the daily diet within the recommended n-6/n-3 ratio is safe. Thus, in addition to serving as an essential fatty acid and a precursor to more bioactive long-chain Omega-3 fatty acid derivatives, ALA has significant functional properties similar to those associated with nutraceuticals. As stated in the 2009 EFSA report, the inclusion of dietary ALA may play a role in reducing the risk of cardiovascular events (CHD and IHD) due to its ant-hypertensive, anti-atherosclerotic, and cardio-protective effects. Recently, there has been promising evidence of its potential anti-inflammatory and anti-proliferative properties, which may extend beyond cardiovascular diseases to include inflammatory and oncological conditions. However, further validation through high-quality studies is required to definitively establish these effects.

4. Patents

Author Contributions: Conceptualization, C.B. and A.M..; writing—original draft preparation, C.B.; writing—review and editing, A.M., G.P.M., M.A,. V.D. and C.A; supervision, A.M and C.A. All authors have read and agreed to the published version of the manuscript.

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