Research Highlights

Benexia® Advanced Seed Nutrition

Chia Oil in Cardiovascular Disease
BENEFITS OF OMEGA-3 ALA

ARRYTHMIA

BLOOD PRESSURE

BLOOD LIPIDS

ISCHEMIC HEART DISEASE

CVD AND CHD MORTALITY

INFLAMMATORY BIOMARKERS

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Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide. Working to lower consumption of saturated fatty acids and trans fatty acids, and increasing the consumption and proportion of plant oils rich in unsaturated fats like mono- and polyunsaturated fats, have been a cornerstone of worldwide dietary guidelines (1,2). Polyunsaturated fats, in particular omega-3 fatty acids, have been a major topic of scientific discovery in revealing their importance to human health.

Alpha linolenic acid (ALA) is the most common essential polyunsaturated fatty acid available in plant sources (3). ALA is an omega-3 precursor of longer carbon chain fatty acids: eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). ALA, the plant omega-3 fatty acid, is found in notable quantities in chia seeds, walnuts, soybeans, canola oil, flaxseeds, and other plant food sources (4). In addition to its role in the production of EPA and DHA, omega-3 ALA provides independent and specific effects on health.

Consumption of dietary ALA has shown to have a significant association to reduced risk factors for cardiovascular disease and decreased mortality risk from cardiovascular and coronary heart diseases (5,6,7).

REPORT SUMMARY

- **Higher ALA intake reduces the risk of ischemic heart disease (also called coronary heart disease) events and is significantly associated with a lower risk of CVD and CHD mortality.**
- **Evidence suggests that ALA intake reduces the risk of ventricular arrhythmia by more than 25 %.**
- **ALA supplementation has shown to help reduce total cholesterol, LDL cholesterol, and triglycerides, and increase HDL cholesterol.**
- **Several investigations have shown the benefticial effects of ALA administered alone or as a component of food in reducing blood pressure.**
- **Epidemiological evidence has shown higher dietary ALA to be associated with lower inflammation, as measured by inflammatory biomarkers.**
- **Higher intakes of ALA have been shown to be associated with lower intima-media thickness (IMT), lower carotid plaque, and to lower coronary artery plaque.**

Cardiovascular Disease (CVD) and Coronary Heart Disease (CHD) Mortality

Higher ALA intake reduces the risk of ischemic heart disease (IHD), also called coronary heart disease (CAD), events and is significantly associated with an 8 % and 11 % lower risk of CVD and CHD mortality, respectively.

Independent scientific investigations have found a significant inverse association between dietary intake of ALA and CVD mortality (5,6). In these studies, researchers reported that a certain quantity of ALA intake (<1.4 g/day) was associated with reduced risk of CHD (8). A recent 2021 meta-analysis found a inverse dose-response association between dietary ALA intake and CVD mortality, such that a 1 g/day increase in ALA intake was associated with a 5 % lower risk of mortality by CVD (5). Additionally, Pan et al. found that higher consumption of ALA as compared to lower ALA intake was associated with a reduced risk of fatal IHD (9). Furthermore, in dose-response analyses, each additional 1 g/day of ALA intake was associated with a 10 % reduction in the risk of fatal IHD (9).

It has also been reported that the association of ALA consumption and IHD risk reduction is different respective to gender. In an investigation by Vedtofte et al. reported among men, an inverse association (not significant) between the intake of ALA and the risk of CHD events and deaths was observed. For each additional gram of ALA consumed, a 15 % lower risk of CHD events (hazard ratio (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) were observed. No consistent association was observed among women (10).

The Lyon Diet Heart Study was a landmark study that demonstrated the efficacy of an ALA-supplemented Mediterranean-type diet on composite measures of IHD recurrence (11). After 46 months, participants in the experimental group who followed a Mediterranean-style diet and were given a canola oil-based margarine containing 4.8 % ALA showed a 50–70 % lower risk of recurrent IHD (12).

Significant inverse associations between blood ALA levels and CHD mortality, and between serum and plasma ALA levels and CVD mortality, have been found in many investigations (5).

Researchers report that part of the variability of findings could be explained in part due to ALA being measured in different tissues. When limiting the analyses specifically to studies that looked at ALA in blood, particularly plasma or serum total ALA, previously non-significant inverse associations between ALA and CVD and CHD mortality became significant (5). One proposed explanation is that ALA blood levels may be more objective biomarkers of circulating ALA levels over the past 1-2 months that reflect the current diet along with dietary ALA metabolism (13). Thus, the results of ALA blood levels in contrast to adipose tissue levels have shown to be more consistent with the results of actual reported dietary ALA intake (5).

Arrhythmia

Evidence suggests that ALA intake reduces the risk of ventricular arrhythmia by 27 %

Two large trials have evaluated ALA supplementation for cardiovascular outcomes, including arrhythmias. In the AlphaOmega trial, in a post hoc analysis in the subgroup of patients with diabetes, a population particularly prone to ventricular arrhythmias and sudden death after MI, ALA supplementation compared with placebo or EPA + DHA led to a significant reduction in arrhythmia-related events (55).

While ALA does not appear to affect atrial arrhythmia, there is evidence in patients with myocardial infarction (MI) that a higher intake of omega-3 PUFA, both marine and plant ALA, is associated with lower premature ventricular beats, suggesting a reduced risk of ventricular arrhythmias (14,15).

Another report from the AlphaOmega trial on patients with diabetes showed a significant reduction in ventricular arrhythmia-related events for the EPA + DHA plus ALA supplementation group compared to placebo, indicating an additive antiarrhythmic effect of plant-derived omega-3 and marine PUFAs (16). The results of the AlphaOmega trial suggest that ALA intake has an antiarrhythmic effect, but more clinical trials are needed to further confirm this.

In other important research on the topic, the Lyon Diet Heart study, in which an ALA-enriched margarine was given to the intervention group, researchers noted that there were too few arrhythmic events to enable strong analysis to be able to report any meaningful findings (12). Additionally, in the most recent and extensive systematic assessment of effects of omega-3 fats on cardiovascular health to date, the evidence suggested that increasing ALA intake appears to reduce risk of arrhythmia (6,7). Although some research shows benefit and the potential for positive impact, others have not, and clearly more research is needed in this area.

Major and Emerging Cardiovascular Risk Factors

DYSLIPIDEMIA

ALA reduces total cholesterol, LDL cholesterol, triglycerides and increased HDL cholesterol

Recent scientific evidence supports the association between intake of polyunsaturated fatty acid PUFAs and decreased risk of dyslipidemia (17). PUFA intake (>19.5 g/day) has been associated with an independent 19 % decrease in the risk of dyslipidemia.

Regarding ALA specifically, different and very recent meta-analyses have examined the effect of ALA intake on the lipid profile in humans, showing significant reductions in total cholesterol, LDL cholesterol and triglycerides, and increases in HDL cholesterol; hence researchers largely concur that ALA supplementation may be regarded as a generally safe, complementary, or alternative approach with clinical relevance in primary cardiovascular disease prevention (18, 19, 20, 21, 22).

In a 2020 meta-analysis, Chen et al. found that compared with EPA and DHA, plant omega-3 ALA significantly reduced total cholesterol, LDL cholesterol, and triglycerides (18).

These lipid-lowering effects are supported by other research that associates the ALA content of the traditional diet of the population and lipid reduction, in particular, in both Asian and European countries, ALA intake is associated with reductions in total cholesterol and LDL cholesterol, with the association more pronounced in Asian countries where higher amounts of ALA are consumed in the traditional diet (20).

The studies to date have looked at the various major sources of ALA in the plant world: chia seeds, walnuts and flaxseeds.

In an Randomized Controlled Trials (Rcts) in an animal model evaluating plasmatic lipid profile effects, the incorporation of ALA from chia seed or chia oil added to the diet for 30 days resulted in a hypolipidemic effect: showing statistically lower total cholesterol (TC) and triglyceride (TAG) values and a higher HDL cholesterol, as well as a TC:HDL ratio, that was significantly lower (21).

In another study, individuals were administered daily with four gastro-resistant capsules for 8 weeks. Each capsule contained 500 mg of cryo-micronized chia seeds and 15 mg of vitamin E. The results showed that the supplementation with chia seed, rich in ALA, showed a significant decrease of triglycerides in serum, -27,5 %; total cholesterol -8 %; and LDL cholesterol, -10.2 %. In addition, there was a significant increase in the content of HDL cholesterol in serum, +5.7 % (23).

The lipids/lipoproteins effects of walnuts, a major source of ALA, were recently evaluated in the largest and longest randomized controlled trial to date, the Walnuts And Healthy Aging (WAHA) study (24). The WAHA trial concluded that participants in the walnut group had significant reductions in total cholesterol, LDL cholesterol, as well as statistically significant reductions in the number of total LDL particles and small LDL particles, both risk factors for CVD.

In a recent study looking at flaxseeds, patients diagnosed with non-alcoholic fatty liver disease who consumed 30 g of flaxseeds daily along with implementing positive lifestyle interventions for 12 weeks showed significantly lowered total cholesterol, TG, and LDL cholesterol; whereas similar results not were achieved in the group receiving positive lifestyle intervention only (25). In another recent meta-analysis of randomized controlled trials (RCTs), flaxseed products, such as flaxseed oil, as a source of ALA, showed a significant decrease in plasma Lp(a) levels, an LDL particle type that has been linked with increased CVD risk (26).

Major and Emerging Cardiovascular Risk Factors

BLOOD PRESSURE

Several investigations have shown the effect of ALA administered alone or as a component of food in reducing blood pressure (BP)

A growing number of studies have shown beneficial impact on blood pressure associated with ALA intake. The FLAX-PAD (FLAX effects in Peripheral Arterial Disease) trial showed large effects of ALA consumption on diastolic and systolic blood pressure in patients with peripheral artery disease. The participants were fed a variety of foods (bagels, muffins, bars, buns, pasta, tea biscuits) containing 30 g of ground flaxseeds or control for 6 months (27). Those consuming the flaxseeds showed a significant reduction of 15 mmHg in SBP and 7 mmHg in DBP. Other studies using flaxseed supplementation for BP outcomes have shown significant reductions in both systolic and diastolic BP. The effects of BP were greater in studies of ≥12 weeks' duration (28).

The association of chia consumption and lower blood pressure has also been described by some researchers. In a study with individuals treated with hypertensive-drugs (MD) and untreated (NM), the subjects consumed 35 g/day of either chia flour or a placebo for 12 weeks. While the placebo group showed no changes in BP, there was a reduction in the mean clinical blood pressure (BP) in the CHIA-MD group (from an average 111.3 down to average 100.1 mmHg) group and the CHIA-NM group showed no reduction in the MBP but did show a decreased systolic BP (146.8 to 137.3 mmHg). The results of this study showed that consumption of chia can help lower BP in hypertensive patients, even in patients previously treated with medications and similarly to patients not taking medications (29).

These results were also accompanied by significantly reduced lipid peroxidation, however markers of inflammation did not show change (29). Increases in lipid peroxidation and decreases in antioxidant protection naturally occur with aging. Peroxidative damage is generally further increased when someone has high blood pressure, which in turn, increases cardiovascular risk.

In patients with type 2 diabetes (T2DM) and hypertension, research has also shown that chia seed adjunct to conventional treatment in individuals with type 2 diabetes may help reduce traditional and non-traditional risk factors for CVD, including a significantly reduced SBP (22, 30).

Other sources of ALA such as walnuts have also been evaluated. The WAHA trial reported that mean systolic BP decreased by 4.6 mmHg in the walnut group (30). Additionally, participants in the walnut group required lower doses of antihypertensive medications than control participants. Finally, in a study conducted in healthy Japanese participants, 6-month supplementation with Perilla frutescens leaf powder (another source of ALA) reported significantly reduced systolic BP among subjects with baseline systolic BP ≥120 mmHg (32).

INFLAMMATORY BIOMARKERS

Epidemiological evidence has shown inverse associations of dietary ALA and plasma inflammatory biomarkers

In a cross-sectional study within the well-known Nurses Study cohort, ALA intake, assessed through validated food frequency questionaires over time, was inversely associated to plasma concentrations of inflammatory markers including C-reactive protein (CRP), IL-6, and E-selectin, after controlling for multiple factors (33).

This inverse association between ALA and proinflammatory biomarkers has not only been observed in healthy people, but similar results have been found in insulin-resistant patients in the secondary prevention of CVD and in patients with type 2 diabetes (34), suggesting that ALA could help lower CRP even in people with a higher initial CRP (35,36). This reduction of CRP concentrations in overweight/obese or high-risk patients with type 2 diabetes has also been observed with chia seed supplementation (22).

In addition to inflammatory markers such as CRP, significant mean reductions ranging from 3.5 % to 11.5 % have been described in granulocytes and monocyte colony-stimulating factors, IFN-γ, IL-1β, IL-6, TNF-α, and E-selectin, after supplementation of walnuts, flaxseeds or chia seeds (37, 38, 39, 22).

Major and Emerging Cardiovascular Risk Factors

ATHEROSCLEROSIS AND ARTERIAL MARKERS

ALA intake has been shown to be inversely related to intima-media thickness (IMT), carotid plaque, and to coronary artery plaque

One of the ways scientists measure cardiovascular risk is through the thickness of the intima-media (IMT) and the plaque of the carotid and femoral arteries by ultrasonography, which are a markers of atherosclerosis, and therefore predictors of cardiovascular events (40).

Several studies in different population groups have evaluated the association between the consumption of ALA in the diet and markers of atherosclerosis. In a subcohort of the large PREDIMED trial, compared with the control group (advice to follow the traditional American Heart Association recommendations for low-fat diet), participants who consumed 30 g/day of mixed nuts (with 15 g of walnuts providing ~1.3 g of ALA) showed a statistically significantly regression of the maximum height of the carotid plate (41).

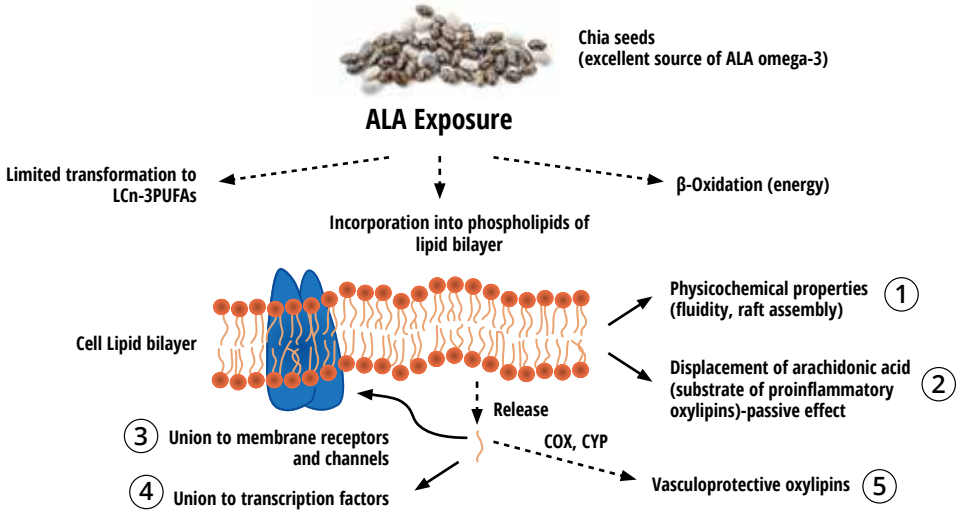
In other research in U.S. populations, ALA intake was shown to be inversely related to IMT and carotid plaque (42) and coronary artery plaque (43). And in a Spanish study on individuals with dyslipidemia, ALA in serum phospholipids was also inversely related to carotid IMT (44) and carotid and femoral plaque burden (45,46). Further, another study in the Chinese population reported that less thickening of the carotid IMT and a lower prevalence of carotid plaque were associated with increased ALA and DHA, but not EPA, in red blood cell membranes (47).

Mechanisms of Action of ALA in Cardiovascular Health

There are a number of proposed mechanisms of action for ALA in the body relative to cardiovascular health, some more well-understood than others, and some still unclear. Related to those involved in the prevention and/or risk reduction of CVD or CHD, it is well established that ALA is a precursor to long-chain omega-3 polyunsaturated fatty acids, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are critically responsible for producing various classes of anti-inflammatory eicosanoids (48).

However, ALA also possesses cardiovascular benefits independent of conversion products as depicted in Figure 1. Researchers in the field have suggested that the intrinsic role of ALA related to its CVD preventive effects includes, among potential others: modulation of ion channels and regulation of gene expression through the peroxisomal proliferation system; and ALA is also converted to oxylipins that help reduce inflammation and improve blood pressure (49,50,51,52,53).

Additionally, ALA contributes to the regulation and modulation of the production of pro-inflammatory eicosanoids from arachidonic acid, which is produced from polyunsaturated omega-6 fats. Unlike omega-3 polyunsaturated fatty acids, the omega--6 polyunsaturated fatty acids, such as linoleic acid and arachidonic acid, favor the production of proinflammatory eicosanoids that play important roles in regulating different homeostatic and inflammatory processes (50). However, epidemiological studies have demonstrated inverse associations between linoleic acid (omega-6) and cardiovascular disease, cancer, and all-cause mortality (48). In general, previous studies have shown that a balanced intake of omega-6 and omega-3 polyunsaturated fatty acids is necessary to reduce the cardiovascular disease risk and maintain good health (53).



Adapted from Figure 1 of Aleix Sala-Vila, Jennifer Fleming, Penny Kris-Etherton, Emilio Ros, Impact of α-Linolenic Acid, the Vegetable ω-3 Fatty Acid, on Cardiovascular Disease and Cognition, Advances in Nutrition, 2022.
From the paper: "FIGURE 1 Proposed primary mechanisms underlying the benefits of dietary ALA. Dietary ALA (obtained from flaxseed, walnuts, chia seeds, canola oil) undergoes fatty acid β-oxidation, convertion to LCn-3PUFAs, and incorporation into cell membrane phospholipids. As occurs with other dietary PUFAs, ALA incorporation into a membrane alters the biophysical membrane properties (1), and partially displaces arachidonic acid, a substrate of proinflammatory lipid mediators (2). Once cleaved from membranes by the action pf phospholipases, ALA binds to specific transmembrane proteins or voltage-gated channels (3), promotes/inhibits gene expression after binding transcription factors (4), and might be converted to anti-inflammatory and antihypertensive lipid mediators by the action of COX and CYP (5). ALA , α-linolenic acid; COX, cyclooxygenase; CYP, cytochrome P450; LCn-3PUFA, long-chain n-3 PUFA."

ALA Consumption Recommendations

ALA is considered an essential fat because the body is unable to produce it endogenously and therefore, it must be consumed through the diet. Based on the Dietary Reference Intakes, daily ALA consumption should provide between 0.6 % and 1.0 % of total energy, i.e. the recommended level, called the Adequate Intake (AI), of ALA is 1.1 g/day for women and 1.6 g/day for men (54). This is the amount determined to establish adequacy to avoid deficiency of this nutrient. Many researchers believe ALA intake above 1.6 g/day could also have benefits for cardiovascular health. For example, in a randomized clinical trial, intervention with ALA at 1.9 g/day was associated with reduced serum low-density lipoprotein and total cholesterol levels in a population with metabolic syndrome and diabetes (55).

According to a non-linear dose-response analysis, ALA intakes between 1.0 and 2.5 g/day are better for the prevention of mortality from coronary heart disease (5). And for CVD, there is some evidence from epidemiological studies of the benefits of ALA at higher intakes (>2 g/day; 0.6–1.0 % of energy) (56). ALA is abundant in several plant foods, including walnuts, chia seeds, flaxseeds, and chia and flaxseed oils.

ALA content of select foods and daily servings needed to meet adequate intakes[1]

Food source of ALA[2]	Amount of ALA per serving.[3] g	Servings per day needed by women to meet recommendarion (1.1g ALA/d)	Servings per day needed by men to meet recommendation (1.6g ALA/d)
Camelina seed oil[4]	4.49	0.24	0.35
Canola oil	1.28	0.86	1.25
Chia seeds	**5.05**	**0.22**	**0.32**
Chia oil	**8.60**	**0.12**	**0.18**
Flaxseed oil	7.26	0.15	0.22
Flaxseeds, ground	6.55	0.17	0.24
Flaxseeds, whole	6.46	0.17	0.25
Olive oil	0.10	11.00	16.00
Perilla seed oil[5]	8.16	0.13	0.20
Pumpkin seeds	0.03	36.67	53.33
Soybean oil	0.95	1.16	1.68
Soybeans (Edamame)	0.28	3.93	5.71
Walnuts, English	2.57	0.43	0.62
Walnut oil	1.41	0.78	1.13

[1] ALA, α-linolenic acid.
[2] Unless otherwise stated, source is USDA ARS (138).
[3] Serving: oil = 1 tbsp (13.6g); seeds/nuts = 1 oz (28.35g); edameme = ½ cup (77.5g).
[4] Data from Ergönül and Özbek (139)
[5] Data from Bondioli et al. (140).

Most of these foods are also rich in bioactive molecules in addition to ALA, which have been proposed as likely contributing to the beneficial effects overall. As a result, foods rich in polyunsaturated fatty acids, especially ALA, should be included on a daily basis for overall nutrition and as part of a heart-healthy diet.

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